US006337206B1

(12) **United States Patent**
Tan et al.

(10) **Patent No.: US 6,337,206 B1**
(45) **Date of Patent: *Jan. 8, 2002**

(54) **NUCLEIC ACID ENCODING MOUSE GALANIN RECEPTOR (GALR2)**

(75) Inventors: **Carina Tan**, Metuchen, NJ (US); **Lee F. Kolakowski, Jr.**, San Antonio, TX (US)

(73) Assignees: **Merck & Co., Inc.**, Rahway, NJ (US); **Board of Regents, The University of Texas System**, Austin, TX (US)

(*) Notice: This patent issued on a continued prosecution application filed under 37 CFR 1.53(d), and is subject to the twenty year patent term provisions of 35 U.S.C. 154(a)(2).

Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **08/993,424**

(22) Filed: **Dec. 18, 1997**

(51) **Int. Cl.**[7] **C12N 5/10**; C12N 15/12
(52) **U.S. Cl.** **435/320.1**; 435/325; 536/23.5
(58) **Field of Search** 536/23.5, 24.31; 435/320.1, 325, 69.1; 530/350

(56) **References Cited**

U.S. PATENT DOCUMENTS

5,972,624 A 10/1999 Smith et al. 435/7.2

FOREIGN PATENT DOCUMENTS

WO WO 97/26853 7/1997
WO WO 97/46681 12/1997
WO WO 98/03548 1/1998

OTHER PUBLICATIONS

Habert–Ortoli, et al. 1994. Proc. Nat. Acad. Sci., USA 91: 9780–9783 Molecular cloning of a functional human galanin receptor.

O'Dowd, B. F. et al. 1995 Genomics 28:84–91. The Cloning and Chromosomal Mapping of Two Novel Human Opioid – Somatostatin–like Receptor Genes, GPR7 and GPR8, Expressed in Discrete Areas of the Brain.

Suke Wang, et al., Federation of European Biochemical Societies Letters, 411 (1997) 225–230; Genomic organization and functional characterization of the mouse GalR1 galanin receptor.

IASP Press (Seattle) Abstracts 8th World Congress on Pain (International Assoc. for the Study of Pain) Aug. 19, 1996, ISBN: 0–931092–17–5, Lib. of Congress 96–77433.

Howard, A. D. et al., Molecular cloning and characterization of a new receptor for galanin, FEBS Letters, vol. 405, pp. 285–290, 1997.

Primary Examiner—Michael Pak
(74) *Attorney, Agent, or Firm*—Sheldon O. Heber; Jack L. Tribble

(57) **ABSTRACT**

A new galanin receptor, GALR2, is described. Also provided are nucleic acids encoding same and various assays to identify ligands particular to said receptor. Ligands so identified are useful for the treatment of obesity, treatment of pain, and treatment of cognitive disorders.

6 Claims, 26 Drawing Sheets

1/26

```
                10                  20                  30                  40
CGCTCCCTCC ACACCTCCAG GGGCAGTGAG CCACTCAAGT 40
CTAAAGCAGA GCGAGTCCCA GGACTTGAGC GCGGGAAGCG 80
AATGGAGTCA GGGTCATTCG ATTGCACCTC TCTCGGCTGC 120
GGGCCGGAGC GGGGTACCAT CCTACACTCT GGGTGCTCCC 160
TCCTCCTCCC GTCCCCCGCG CACCCCTGCC CTGGCTCCTG 200

          210                 220                 230                 240
GAGCTCGGCA GTCTCGCTGG GGCGCTGCAG CGAGGGAGCA 240
GCGTGCTCAC CAAGACCCGG ACAGCTGCGG GAGCGGCGTC 280
CACTTTGGTG ATACCATGAA TGGCTCCGGC AGCCAGGGCG 320
CGGAGAACAC GAGCCAGGAA GGCGGTAGCG GCGGCTGGCA 360
GCCTGAGGCG GTCCTTGTAC CCCTATTTTT CGCGCTCATC 400

          410                 420                 430                 440
TTCCTCGTGG GCACCGTGGG CAACGCGCTG GTGCTGGCGG 440
TGCTGCTGCG CGGCGGCCAG GCGGTCAGCA CCACCAACCT 480
GTTCATCCTC AACCTGGGCG TGGCCGACCT GTGTTTCATC 520
CTGTGCTGCG TGCCTTTCCA GGCCACCATC TACACCCTGG 560
ACGACTGGGT GTTCGGCTCG CTGCTCTGCA AGGCTGTTCA 600

          610                 620                 630                 640
TTTCCTCATC TTTCTCACTA TGCACGCCAG CAGCTTCACG 640
CTGGCCGCCG TCTCCCTGGA CAGGTAAAGG ACCCAGAAAG 680
AAACATCCAG TATGCCCGGA GGGATCTTGA CTGGAAAAGA 720
CTGAATCCTG GTCTGGTGAC CTTAGTTCCC TGCCCTTTCA 760
CATCACTTGG ACATTCCCAC AGAAGAGCGG TGAAGAGGCG 800

          810                 820                 830                 840
GTGGTCCTTA TTCTCCTCTG GTTTCCACTG AGTGCAACAT 840
GTGCGTCCTG AGTACGCTGG AGGGACTCAC AAAATTTCAG 880
CTTTCTTTAG GAGTTTCCTT GCTGTAGTTT GACCCAAGTC 920
TTCTCCAGGT TTCTGTCAGA ACCTCAGGCA TGAGGGATCT 960
GCCTCCCCTG GTTGTCACCA GAGGATAACA ATCACTGCCC 1000

          1010                1020                1030                1040
CCAGAAATCC AGACAGATTC TACAACTTTT AGTCTTCGGT 1040
GTTTTGGGGG TGCCCCTTCA CGTGGAGTAG GTCGGTGGCC 1080
ACATTCCCAG GAGTGACAAT AGCCTAGCAG TGAATCCTCT 1120
CGCTTAGCTG ATGCCCCCCC ACTGTCCCCA CAGGTATCTG 1160
GCCATCCGCT ACCCGCTGCA CTCCCGAGAG TTGCGCACAC 1200
```

FIG. 1A

```
      1210        1220        1230        1240
CTCGAAACGC GCTGGCCGCC ATCGGGCTCA TCTGGGGGCT 1240
AGCACTGCTC TTCTCCGGGC CCTACCTGAG CTACTACCGT 1280
CAGTCGCAGC TGGCCAACCT GACAGTATGC CACCCAGCAT 1320
GGAGCGCACC TCGACGTCGA GCCATGGACC TCTGCACCTT 1360
CGTCTTTAGC TACCTGCTGC CAGTGCTAGT CCTCAGTCTG 1400

      1410        1420        1430        1440
ACCTATGCGC GTACCCTGCG CTACCTCTGG CGCACAGTCG 1440
ACCCGGTGAC TGCAGGCTCA GGTTCCCAGC GCGCCAAACG 1480
CAAGGTGACA CGGATGATCA TCATCGTGGC GGTGCTTTTC 1520
TGCCTCTGTT GGATGCCCCA CCACGCGCTT ATCCTCTGCG 1560
TGTGGTTTGG TCGCTTCCCG CTCACGCGTG CCACTTACGC 1600

      1610        1620        1630        1640
GTTGCGCATC CTTTCACACC TAGTTTCCTA TGCCAACTCC 1640
TGTGTCAACC CCATCGTTTA CGCTCTGGTC TCCAAGCATT 1680
TCCGTAAAGG TTTCCGCAAA ATCTGCGCGG GCCTGCTGCG 1720
CCCTGCCCCG AGGCGAGCTT CGGGCCGAGT GAGCATCCTG 1760
GCGCCTGGGA ACCATAGTGG CAGCATGCTG GAACAGGAAT 1800

      1810        1820        1830        1840
CCACAGACCT GACACAGGTG AGCGAGGCAG CCGGGCCCCT 1840
TGTCCCACCA CCCGCACTTC CCAACTGCAC AGCCTCGAGT 1880
AGAACCCTGG ATCCGGCTTG TTAAAGGACC AAAGGGCATC 1920
TAACAGCTTC TAGACAGTGT GGCCCGAGGA TCCCTGGGGG 1960
TTATGCTTGA ACGTTACAGG GTTGAGGCTA AAGACTGARG 2000

      2010        2020        2030        2040
ATTGATTGTA GGGAACCTCC AGTTATTAAA CGGTGCGGAT 2040
TGCTAGAGGG TGGCATAGTC CTTCAATCCT GGCACCCGAA 2080
AAGCAGATGC AGGAGCAGGA GCAGGAGCAA AGCCAGCCAT 2120
GGAGTTTGAG GCCTGCTTGA ACTACCTGAG ATCCAATAAT 2160
AAAACATTTC ATATGCTGTG AAAAAAAAAA AAAAAAAAAA 2200
```

FIG. 1B

```
                10                  20                  30                  40
                |                   |                   |                   |
ATGAATGGCT CCGGCAGCCA GGGCGCGGAG AACACGAGCC 40
AGGAAGGCGG TAGCGGCGGC TGGCAGCCTG AGGCGGTCCT 80
TGTACCCCTA TTTTTCGCGC TCATCTTCCT CGTGGGCACC 120
GTGGGCAACG CGCTGGTGCT GGCGGTGCTG CTGCGCGGCG 160
GCCAGGCGGT CAGCACCACC AACCTGTTCA TCCTCAACCT 200

                210                 220                 230                 240
                |                   |                   |                   |
GGGCGTGGCC GACCTGTGTT TCATCCTGTG CTGCGTGCCT 240
TTCCAGGCCA CCATCTACAC CCTGGACGAC TGGGTGTTCG 280
GCTCGCTGCT CTGCAAGGCT GTTCATTTCC TCATCTTTCT 320
CACTATGCAC GCCAGCAGCT TCACGCTGGC CGCCGTCTCC 360
CTGGACAGGT AAAGGACCCA GAAAGAAACA TCCAGTATGC 400

                410                 420                 430                 440
                |                   |                   |                   |
CCGGAGGGAT CTTGACTGGA AAAGACTGAA TCCTGGTCTG 440
GTGACCTTAG TTCCCTGCCC TTTCACATCA CTTGGACATT 480
CCCACAGAAG AGCGGTGAAG AGGCGGTGGT CCTTATTCTC 520
CTCTGGTTTC CACTGAGTGC AACATGTGCG TCCTGAGTAC 560
GCTGGAGGGA CTCACAAAAT TTCAGCTTTC TTTAGGAGTT 600

                610                 620                 630                 640
                |                   |                   |                   |
TCCTTGCTGT AGTTTGACCC AAGTCTTCTC CAGGTTTCTG 640
TCAGAACCTC AGGCATGAGG GATCTGCCTC CCCTGGTTGT 680
CACCAGAGGA TAACAATCAC TGCCCCCAGA AATCCAGACA 720
GATTCTACAA CTTTTAGTCT TCGGTGTTTT GGGGGTGCCC 760
CTTCACGTGG AGTAGGTCGG TGGCCACATT CCCAGGAGTG 800

                810                 820                 830                 840
                |                   |                   |                   |
ACAATAGCCT AGCAGTGAAT CCTCTCGCTT AGCTGATGCC 840
CCCCCACTGT CCCCACAGGT ATCTGGCCAT CCGCTACCCG 880
CTGCACTCCC GAGAGTTGCG CACACCTCGA AACGCGCTGG 920
CCGCCATCGG GCTCATCTGG GGGCTAGCAC TGCTCTTCTC 960
CGGGCCCTAC CTGAGCTACT ACCGTCAGTC GCAGCTGGCC 1000
```

FIG. 2A

1010 1020 1030 1040

AACCTGACAG TATGCCACCC AGCATGGAGC GCACCTCGAC 1040
GTCGAGCCAT GGACCTCTGC ACCTTCGTCT TTAGCTACCT 1080
GCTGCCAGTG CTAGTCCTCA GTCTGACCTA TGCGCGTACC 1120
CTGCGCTACC TCTGGCGCAC AGTCGACCCG GTGACTGCAG 1160
GCTCAGGTTC CCAGCGCGCC AAACGCAAGG TGACACGGAT 1200

1210 1220 1230 1240

GATCATCATC GTGGCGGTGC TTTTCTGCCT CTGTTGGATG 1240
CCCCACCACG CGCTTATCCT CTGCGTGTGG TTTGGTCGCT 1280
TCCCGCTCAC GCGTGCCACT TACGCGTTGC GCATCCTTTC 1320
ACACCTAGTT TCCTATGCCA ACTCCTGTGT CAACCCCATC 1360
GTTTACGCTC TGGTCTCCAA GCATTTCCGT AAAGGTTTCC 1400

1410 1420 1430 1440

GCAAAATCTG CGCGGGCCTG CTGCGCCCTG CCCCGAGGCG 1440
AGCTTCGGGC CGAGTGAGCA TCCTGGCGCC TGGGAACCAT 1480
AGTGGCAGCA TGCTGGAACA GGAATCCACA GACCTGACAC 1520
AGGTGAGCGA GGCAGCCGGG CCCCTTGTCC CACCACCCGC 1560
ACTTCCCAAC TGCACAGCCT CGAGTAGAAC CCTGGATCCG 1600

1610 1620 1630 1640

GCTTGTTAAA GGACCAAAGG GCATCTAACA GCTTCTAGAC 1640
AGTGTGGCCC GAGGATCCCT GGGGGTTATG CTTGAACGTT 1680
ACAGGGTTGA GGCTAAAGAC TGAGATTGAT TGTAGGGAAC 1720
CTCCAGTTAT TAAACGGTGC GGATTGCTAG AGGGTGGCAT 1760
AGTCCTTCAA TCCTGGCACC CGAAAAGCAG ATGCAGGAGC 1800

1810 1820 1830 1840

AGGAGCAGGA GCAAAGCCAG CCATGGAGTT TGAGGCCTGC 1840
TTGAACTACC TGAGATCCAA TAATAAAACA TTTCATATGC 1880
TGTGAAAAAA AAAAAAAAAA AAAA 1904

FIG. 2B

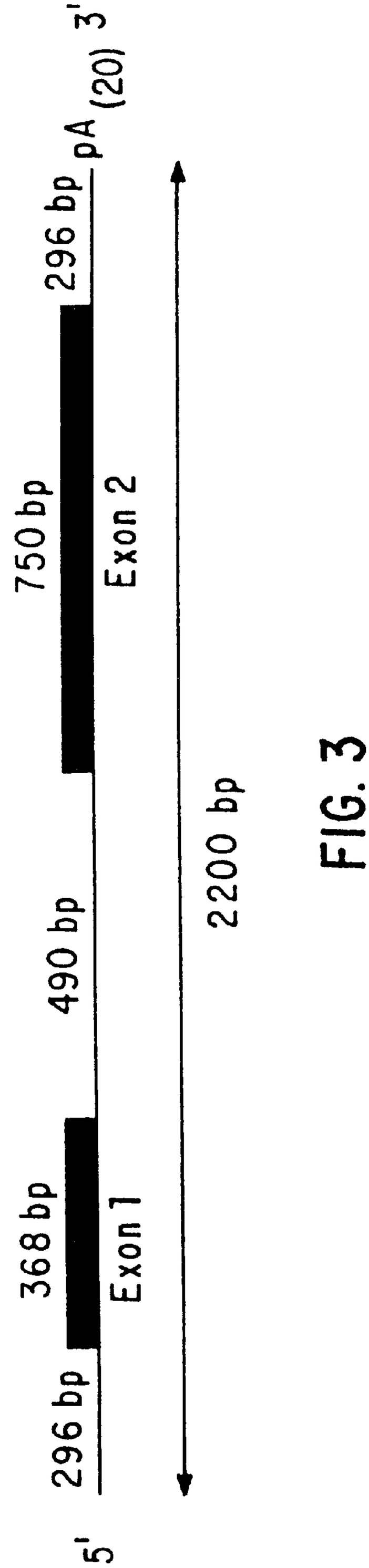

FIG. 3

```
  1  ATG AAT GGC TCC GGC AGC CAG GGC GCG GAG AAC ACG AGC CAG GAA GGC GGT AGC GGC GGC TGG CAG CCT GAG GCG   75
  1  M   N   G   S   G   S   Q   G   A   E   N   T   S   Q   E   G   G   S   G   G   W   Q   P   E   A   25

 76  GTC CTT GTA CCC CTA TTT TTC GCG CTC ATC TTC CTC GTG GGC ACC GTG GGC AAC GCG CTG GTG CTG GCG GTG CTG  150
 26  V   L   V   P   L   F   F   A   L   I   F   L   V   G   T   V   G   N   A   L   V   L   A   V   L   50

151  CTG CGC GGC GGC CAG GCG GTC AGC ACC ACC AAC CTG TTC ATC CTC AAC CTG GGC GTG GCC GAC CTG TGT TTC ATC  225
 51  L   R   G   G   Q   A   V   S   T   T   N   L   F   I   L   N   L   G   V   A   D   L   C   F   I   75

226  CTG TGC TGC GTG CCT TTC CAG GCC ACC ATC TAC ACC CTG GAC GAC TGG GTG TTC GGC TCG CTG CTC TGC AAG GCT  300
 76  L   C   C   V   P   F   Q   A   T   I   Y   T   L   D   D   W   V   F   G   S   L   L   C   K   A  100

301  GTT CAT TTC CTC ATC TTT CTC ACT ATG CAC GCC AGC AGC TTC ACG CTG GCC GCC GTC TCC CTG GAC AG          368
101  V   H   F   L   I   F   L   T   M   H   A   S   S   F   T   L   A   A   V   S   L   D   R       123

369  gtaaaggacccagaaagaaacatccagtatgcccggagggatcttgactggaaaagactgaatcctggtctggtgacctt
449  agttccctgccctttcacatcacttggacattcccacagaagagcggtgaagaggcggtggtccttattctcctctggtt
529  tccactgagtgcaacatgtgcgtcctgagtacgctggagggactcacaaaatttcagctttctttaggagtttccttgct
609  gtagtttgacccaagtcttctccaggtttctgtcagaacctcaggcatgagggatctgcctcccctggttgtcaccagag
689  gataacaatcactgcccccagaaatccagacagattctacaacttttagtcttcggtgttttgggggtgccccttcacgt
769  ggagtaggtcggtggccacattcccaggagtgacaatagcctagcagtgaatcctctcgcttagctgatgcccccccact
849  gtccccacag

859  G TAT CTG GCC ATC CGC TAC CCG CTG CAC TCC CGA GAG TTG CGC ACA CCT CGA AAC GCG CTG GCC GCC ATC GGG     931
124    Y   L   A   I   R   Y   P   L   H   S   R   E   L   R   T   P   R   N   A   L   A   A   I   G   147

932  CTC ATC TGG GGG CTA GCA CTG CTC TTC TCC GGG CCC TAC CTG AGC TAC TAC CGT CAG TCG CAG CTG GCC AAC CTG  1006
148  L   I   W   G   L   A   L   L   F   S   G   P   Y   L   S   Y   Y   R   Q   S   Q   L   A   N   L   50

1007  ACA GTA TGC CAC CCA GCA TGG AGC GCA CCT CGA CGT CGA GCC ATG GAC CTC TGC ACC TTC GTC TTT AGC TAC CTG  1081
151   T   V   C   H   P   A   W   S   A   P   R   R   R   A   M   D   L   C   T   F   V   F   S   Y   L  172

1082  CTG CCA GTG CTA GTC CTC AGT CTG ACC TAT GCG CGT ACC CTG CGC TAC CTC TGG CGC ACA GTC GAC CCG GTG ACT  1156
173   L   P   V   L   V   L   S   L   T   Y   A   R   T   L   R   Y   L   W   R   T   V   D   P   V   T  222
```

FIG.3A

```
1157  GCA GGC TCA GGT TCC CAG CGC GCC AAA CGC AAG GTG ACA CGG ATG ATC ATC ATC GTG GCG GTG CTT TTC TGC CTC  1231
 223  A   G   S   G   S   Q   R   A   K   R   K   V   T   R   M   I   I   I   V   A   V   L   F   C   L    247

1232  TGT TGG ATG CCC CAC CAC GCG CTT ATC CTC TGC GTG TGG TTT GGT CGC TTC CCG CTC ACG CGT GCC ACT TAC GCG  1306
 248  C   W   M   P   H   H   A   L   I   L   C   V   W   F   G   R   F   P   L   T   R   A   T   Y   A    272

1307  TTG CGC ATC CTT TCA CAC CTA GTT TCC TAT GCC AAC TCC TGT GTC AAC CCC ATC GTT TAC GCT CTG GTC TCC AAG  1381
 273  L   R   I   L   S   H   L   V   S   Y   A   N   S   C   V   N   P   I   V   Y   A   L   V   S   K    297

1382  CAT TTC CGT AAA GGT TTC CGC AAA ATC TGC GCG GGC CTG CTG CGC CCT GCC CCG AGG CGA GCT TCG GGC CGA GTG  1456
 298  H   F   R   K   G   F   R   K   I   C   A   G   L   L   R   P   A   P   R   R   A   S   G   R   V    322

1457  AGC ATC CTG GCG CCT GGG AAC CAT AGT GGC AGC ATG CTG GAA CAG GAA TCC ACA GAC CTG ACA CAG GTG AGC GAG  1531
 323  S   I   L   A   P   G   N   H   S   G   S   M   L   E   Q   E   S   T   D   L   T   Q   V   S   E    347

1532  GCA GCC GGG CCC CTT GTC CCA CCA CCC GCA CTT CCC AAC TGC ACA GCC TCG AGT AGA ACC CTG GAT CCG GCT TGT  1606
 348  A   A   G   P   L   V   P   P   P   A   L   P   N   C   T   A   S   S   R   T   L   D   P   A   C    372

1607  TAA                                                                                              1609
       *
```

FIG.3B

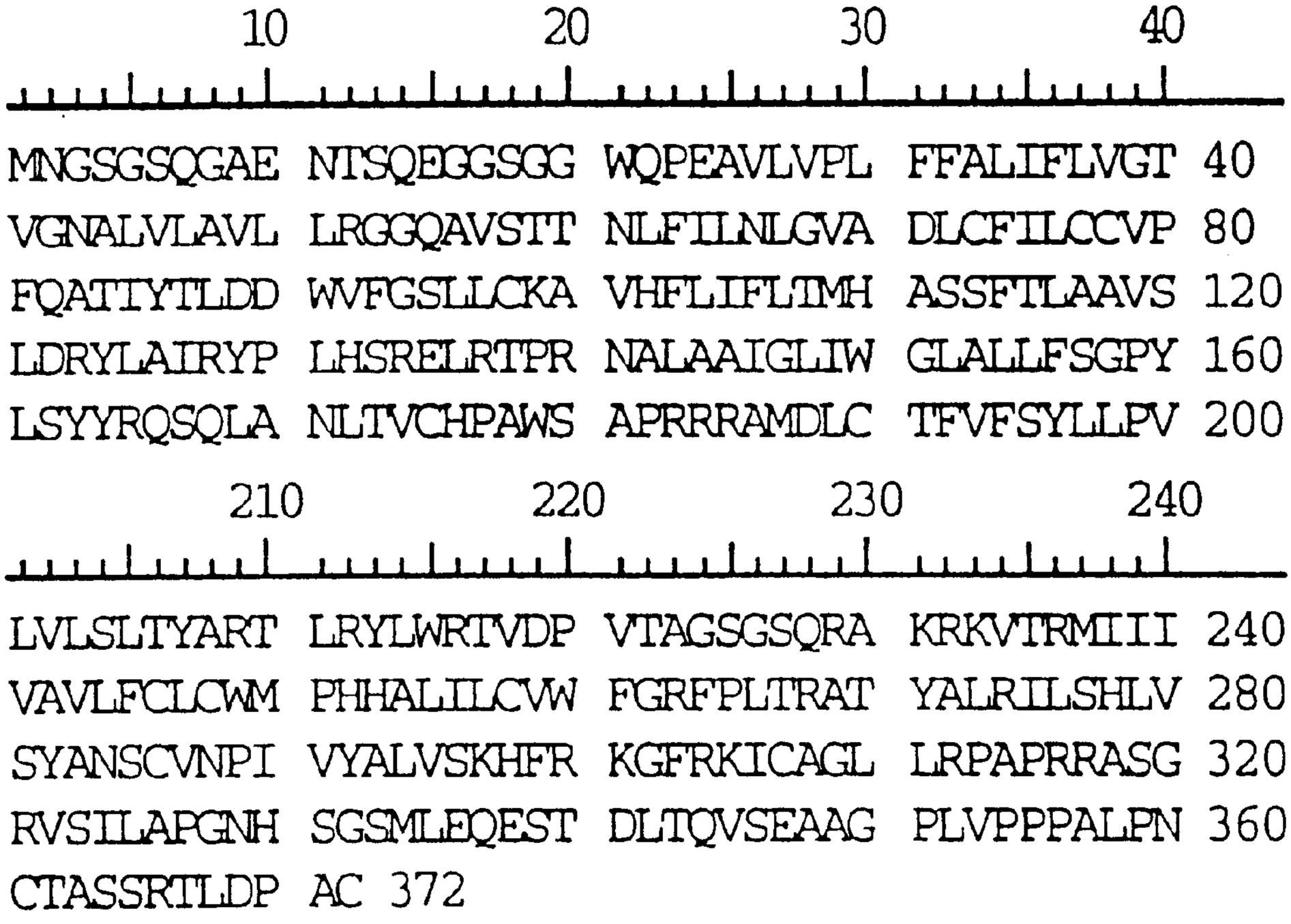
10
20
30
40
MNGSGSQGAE NITSQEGGSGG WQPEAVLVPL FFALIFLVGT 40
VGNALVLAVL LRGGQAVSTT NLFILNLGVA DLCFILCCVP 80
FQATIYTLDD WVFGSLLCKA VHFLIFLTMH ASSFTLAAVS 120
LDRYLAIRYP LHSRELRTPR NALAAIGLIW GLALLFSGPY 160
LSYYRQSQLA NLTVCHPAWS APRRRAMDLC TFVFSYLLPV 200
210
220
230
240
LVLSLTYART LRYLWRTVDP VTAGSGSQRA KRKVTRMIII 240
VAVLFCLCWM PHHALILCVW FGRFPLTRAT YALRILSHLV 280
SYANSCVNPI VYALVSKHFR KGFRKICAGL LRPAPRRASG 320
RVSILAPGNH SGSMLEQEST DLTQVSEAAG PLVPPPALPN 360
CTASSRTLDP AC 372

FIG. 4

```
ratgal1p    1   MELAPVNLSEGNGSDPEPPAEPRPLFGIGVENF  33
ratgal2p    1   -------MNGSGSQGAENTSQEGGSGGWQPEAV  26

ratgal1p   34   ITLVVFGLIFAMGVLGNSLVITVLARSKPGKPR  66
ratgal2p   27   LVPLFFALIFLVGTVGNALVLAVLLRG--GQAV  57

ratgal1p   67   STTNLFILNLSIADLAYLLFCIPFQATVYALPT  99
ratgal2p   58   STTNLFILNLGVADLCFILCCVPFQATIYTLDD  90

ratgal1p  100   WVLGAFICKFIHYFFTVSMLVSIFTLAAMSVDR 132
ratgal2p   91   WVFGSLLCKAVHFLIFLTMHASSFTLAAVSLDR 123

ratgal1p  133   YVAIVHSRRSSSLRVSRNALLGVGFIWALSIAM 165
ratgal2p  124   YLAIRYPLHSRELRTPRNALAAIGLIWGLALLF 156

ratgal1p  166   ASPVAYYQRLFHRDSNQTFCWEHWPNQLHKKAY 198
ratgal2p  157   SGPYLSYYRQSQL-ANLTVCHPAWSAP-RRRAM 187

ratgal1p  199   VVCTFVFGYLLPLLLICFCYAKVLNHLHKKLKN 231
ratgal2p  188   DLCTFVFSYLLPVLVLSLTYARTLRYLWRTVDP 220
```

FIG. 5A

```
ratgal1p   232  M - - S K K S E A S K K K T A Q T V L V V V V F G I S W L P H H  262
ratgal2p   221  V T A G S G S Q R A K R K V T R M I I I V A V L F C L C W M P H H  253

ratgal1p   263  V I H L W A E F G A F P L T P A S F F F R I T A H C L A Y S N S S  295
ratgal2p   254  A L I L C V W F G R F P L T R A T Y A L R I L S H L V S Y A N S C  286

ratgal1p   296  V N P I I Y A F L S E N F R K A Y K Q V F K C R V C N E S P H G D  328
ratgal2p   287  V N P I V Y A L V S K H F R K G F R K I C A G L L R P A P R R A S  319

ratgal1p   329  A K - - - - - - - - E K N R I D T P P S T N C T H V - - - - - - -  346
ratgal2p   320  G R V S I L A P G N H S G S M L E Q E S T D L T Q V S E A A G P L  352

ratgal2p   353  V P P P A L P N C T A S S R T L D P A C                          373
```

FIG. 5B

1
TGCGGACCACCACCAACTTGTACCTGGGCA 30

GCATGGCCGTGTCCGACCTACTCATCCTGC 60

TCGGGCTGCCGTTCGACCTGTACCGCCTCT 90

GGCGCTCGCGGCCCTGGGTGTTCGGGCCGC 120

TGCTCTGCCGCCTGTCCCTCTACGTGGGCG 150

AGGGCTGCACCTACGCCACGCTGCTGCACA 180

TGACCGCGCTCAGCGTCGAGCGCTACCTGG 210

CCATCTGCCGCCCGCTCCGCGCCCGCGTCT 240

TGGTCACCCGGCGCCGCGTCCGCGCGCTCA 270

TCGCTGTGCTCTG 283

FIG.6

gagctcggaagcaggtacaagcgccactctccgcctgcgccgtggaatgcgcgccgggacc
antccgcagcccttcccccagcgccgccggccgctgctggggacaacctcgccctcctgtn
tcttgctcctcctcctgaccccagcgcacccccatccccgccccagatgaggcaaggctcc
ctccgccttcagcccggcagagtcgcactaggagttgcagcggccgcagccccgggagctt
cccgctcgcggagacccagacggctgcaggagcccgggcagcctcggggtcagcggcaccA
TGAACGTCTCGGGCTGCCCAGGGGCCGGGAACGCGAGCCAGGCGGGCGGCGGGGGAGGCTG
GCACCCCGAGGCGGTCATCGTGCCCCTGCTCTTCGCGCTCATCTTCCTCGTGGGCACCGTG
GGCAACACGCTGGTGCTGGCGGTGCTGCTGCGCGGCGGCCAGGCGGTCAGCACTACCAACC
TGTTCATCCTTAACCTGGGCGTGGCCGACCTGTGTTTCATCCTGTGCTGCGTGCCCTTCCA
GGCCACCATCTACACCCTGGACGGCTGGGTGTTCGGCTCGCTGCTGTGCAAGGCGGTGCAC
TTCCTCATCTTCCTCACCATGCACGCCAGCAGCTTCACGCTGGCCGCCGTCTCCCTGGACA
Ggtgagccagcgccttggcctccctgggagatgggcatccacgcgggggatggagcgggag
gcgggactggggaccaagaagggacgcgcagagtgggacaggacactaagaaggcagtgga
agacaagcgggcgcggaggaggaaaaagaggaataagaatgggggaccgtggtgtccctcg
gttagatgcgtcctggggcctggaagcctggagaatgtggctctccagcgccgcccgtgcc
tgacaacgcgcagcgtttcccagtacgacgcgtttgtgcgcgttcatctcgcttgagctta
atgccctccgtgagggtgggataggacaaagtgcccaatatacagaagagttgagttcctа
agtaactcgctcagagtcgccagccaagggatcgggtgcgttgaagtgaccgtctgtctcc
tgcagccaacttcaggcgcctccactgcgctcgcctccaagccacggtttggttggttggt
gcagctggctcaggtccaggctgtggatcttgggtcctttgcaaggatccactccggagtc
ccagcgagcgtgcctaaaggtccctagctcagtcccagcccactctgcctctcgcctccaa
acaaaacaaaaacaaaataaaatccaaaacaagtggggcgggagaggaagcgttgccctgg
ggttcttcctcccagccagaggagagcgaagagacgcacattcgggagagccgccgggact
caggtggagcttgaaaggacactgggatggtttccctggggaggaaatccgggtatttccc
ctctccatcctctggaaaaacagagaggcgaggccagactgcccccacacctcctgtagcc
actgagcgcgaagtgcgttggttccgagcgcgctggtgggatccacaaagctcgcattctc
tcaggaatcccctgagaaattaactgtcccttgcccaacatgtcttctccaggctgtctgc
tagagcctcaggcgcctccgccctccctcccgcggcaccgtcaccagtgggtagtcacagc
ctcccggagcccatagccggttctccaacctttagtcttcagtggctttggggtgccctct
cagtggagactgtggttgcagtccccgggggcagcgggagaatggcttgaaggcacacctt
tcctgctgccggcccgccccatttccagcgtccgctgagtgtctgggacacgctgggaggc
ccccacctccgccctcacgccgagcctcacccccacctcctctgtgtgcggtgtaaccatg
cgctaaggaccttccttgagagcagccttgggaccgaggtgcaggggtcgcggccctccag
catgaatgtgcccgctcagccgacgtctcccttcccggtctgaccgcagGTATCTGGCCAT
CCGCTACCCGCTGCACTCCCGCGAGCTGCGCACGCCTCGAAACGCGCTGGCAGCCATCGGG
CTCATCTGGGGGCTGTCGCTGCTCTTCTCCGGGCCCTACCTGAGCTACTACCGCCAGTCGC

FIG.7A

AGCTGGCCAACCTGACCGTGTGCCATCCCGCGTGGAGCGCCCCTCGCCGCCGCGCCATGGA
CATCTGCACCTTCGTCTTCAGCTACCTGCTTCCTGTGCTGGTTCTCGGCCTGACCTACGCG
CGCACCTTGCGCTACCTCTGGCGCGCCGTCGACCCGGTGGCCGCGGGCTCGGGTGCCCGGC
GCGCCAAGCGCAAGGTGACACGCATGATCCTCATCGTGGCCGCGCTCTTCTGCCTCTGCTG
GATGCCCCACCACGCGCTCATCCTCTGCGTGTGGTTCGGCCAGTTCCCGCTCACGCGCGCC
ACTTATGCGCTTCGCATCCTCTCGCACCTGGTCTCCTACGCCAACTCCTGCGTCAACCCCA
TCGTTTACGCGCTGGTCTCCAAGCACTTCCGCAAAGGCTTCCGCACGATCTGCGCGGGCCT
GCTGGGCCGTGCCCCAGGCCGAGCCTCGGGCCGTGTGTGCGCTGCCGCGCGGGGCACCCAC
AGTGGCAGCGTGTTGGAGCGCGAGTCCAGCGACCTGTTGCACATGAGCGAGGCGGCGGGGG
CCCTTCGTCCCTGCCCCGGCGCTTCCCAGCCATGCATCCTCGAGCCCTGTCCTGGCCCGTC
CTGGCAGGGCCCAAAGGCAGGCGACAGCATCCTGACGGTTGATGTGGCCTGAaagcactta
gcgggcgcgctgggatgtcacagagttggagtcattgttgggggaccgtggggagagcttt
gcctgttaataaaacgcacaaaccatttcacacacagtgacagcgctgtttcgcgtttctc
attgtcttgagattctgggaggaagcctctggggcttcacagaggggctccctaggggtaa
gtgcaggacccttgcagagctaccaggaaagagggctgatcacacctcaggcagccgggt
tacaatccgcataaaaatctgagtctggggagcgtgcgacagaggcaggcagattgtttaa
ggcgttcgataaagtcggttgatgacagacacagatgtgtgttcccagccgcatttgtgct
ctggtgtgtgacaggtctgtccttgcctgctttcagctcccagggcccctttgagtctggg
cagcccagtcagtccccgtccatttttggccttagcttttccttccctggctacatctggg
ccaggatcaagtctccagcagctgtttcactcccc

FIG.7B

ATGAACGTCTCGGGCTGCCCAGGGGCCGGGAACGCGAGCCAGGCGGGCGGCGGGGGAGGCT
GGCACCCCGAGGCGGTCATCGTGCCCCTGCTCTTCGCGCTCATCTTCCTCGTGGGCACCGT
GGGCAACACGCTGGTGCTGGCGGTGCTGCTGCGCGGCGGCCAGGCGGTCAGCACTACCAAC
CTGTTCATCCTTAACCTGGGCGTGGCCGACCTGTGTTTCATCCTGTGCTGCGTGCCCTTCC
AGGCCACCATCTACACCCTGGACGGCTGGGTGTTCGGCTCGCTGCTGTGCAAGGCGGTGCA
CTTCCTCATCTTCCTCACCATGCACGCCAGCAGCTTCACGCTGGCCGCCGTCTCCCTGGAC
AGGTATCTGGCCATCCGCTACCCGCTGCACTCCCGCGAGCTGCGCACGCCTCGAAACGCGC
TGGCAGCCATCGGGCTCATCTGGGGGCTGTCGCTGCTCTTCTCCGGGCCCTACCTGAGCTA
CTACCGCCAGTCGCAGCTGGCCAACCTGACCGTGTGCCATCCCGCGTGGAGCGCCCCTCGC
CGCCGCGCCATGGACATCTGCACCTTCGTCTTCAGCTACCTGCTTCCTGTGCTGGTTCTCG
GCCTGACCTACGCGCGCACCTTGCGCTACCTCTGGCGCGCCGTCGACCCGGTGGCCGCGGG
CTCGGGTGCCCGGCGCGCCAAGCGCAAGGTGACACGCATGATCCTCATCGTGGCCGCGCTC
TTCTGCCTCTGCTGGATGCCCCACCACGCGCTCATCCTCTGCGTGTGGTTCGGCCAGTTCC
CGCTCACGCGCGCCACTTATGCGCTTCGCATCCTCTCGCACCTGGTCTCCTACGCCAACTC
CTGCGTCAACCCCATCGTTTACGCGCTGGTCTCCAAGCACTTCCGCAAAGGCTTCCGCACG
ATCTGCGCGGGCCTGCTGGGCCGTGCCCCAGGCCGAGCCTCGGGCCGTGTGTGCGCTGCCG
CGCGGGGCACCCACAGTGGCAGCGTGTTGGAGCGCGAGTCCAGCGACCTGTTGCACATGAG
CGAGGCGGCGGGGGCCCTTCGTCCCTGCCCCGGCGCTTCCCAGCCATGCATCCTCGAGCCC
TGTCCTGGCCCGTCCTGGCAGGGCCCAAAGGCAGGCGACAGCATCCTGACGGTTGATGTGG
CCTGA

FIG.8

```
gca Ala(A) 2 # cag Gln(Q)   8 # uug Leu(L)  3  # uaa Ter(.)  0
gcc Ala(A) 23 # --- Gln(Q)  8 # --- Leu(L)  56 # uag Ter(.)  0
gcg Ala(A) 19 # gaa Glu(E)  0 # aaa Lys(K)  1  # uga Ter(.)  1
gcu Ala(A)  2 # gag Glu(E)  6 # aag Lys(K)  5  # --- Ter(.)  1
--- Ala(A) 46 # --- Glu(E)  6 # --- Lys(K)  6  # aca Thr(T)  1
aga Arg(R)  0 # gga Gly(G)  1 # aug Met(M)  6  # acc Thr(T) 10
agg Arg(R)  1 # ggc Gly(G) 25 # --- Met(M)  6  # acg Thr(T)  6
cga Arg(R)  2 # ggg Gly(G)  7 # uuc Phe(F) 17  # acu Thr(T)  2
cga Arg(R) 19 # ggu Gly(G)  1 # uuu Phe(F)  0  # --- Thr(T) 19
cgg Arg(R)  2 # --- Gly(G) 34 # --- Phe(F) 17  # ugg Trp(W)  8
cgu Arg(R)  3 # cac His(H) 10 # cca Pro(P)  4  # --- Trp(W)  8
--- Arg(R) 27 # cau His(H)  1 # ccc Pro(P) 10  # uac Tyr(Y) 10
aac Asn(N)  9 # --- His(H) 11 # ccg Pro(P)  4  # uau Tyr(Y)  2
aau Asn(N)  0 # aua Ile(I)  0 # ccu Pro(P)  4  # --- Tyr(Y) 12
--- Asn(N)  9 # auc Ile(I) 18 # --- Pro)P) 22  # gau Val(V)  0
gac Asp(D)  7 # auu Ile(I)  0 # agc Ser(S) 11  # guc Val(V)  9
gau Asp(D)  1 # --- Ile(I) 18 # agu Ser(S)  1  # gug Val(V) 18
--- Asp(D)  8 # cua Leu(L)  0 # uca Ser(S)  0  # guu Val(V)  3
ugc Cys(C) 14 # cuc Leu(L) 17 # ucc Ser(S)  9  # --- Val(V) 30
ugu Cys(C)  2 # cug Leu(L) 32 # ucg Ser(S)  7  # nnn ???(X)  0
--- Cys(C) 16 # cuu Leu(L)  4 # ucu Ser(S)  0  # TOTAL      388
```

FIG.9A

MNVSGCPGAGNASQAGGGGGWHPEAVIVPLLFALIFLVGTVGNTL
VLAVLLRGGQAVSTTNLFILNLGVADLCFILCCVPFQATIYTLDGWV
FGSLLCKAVHFLIFLTMHASSFTLAAVSLDRYLAIRYPLHSRELRTPR
NALAAIGLIWGLSLLFSGPYLSYYRQSQLANLTVCHPAWSAPRRRA
MDICTFVFSYLLPVLVLGLTYARTLRYLWRAVDPVAAGSGARRAK
RKVTRMILIVAALFCLCWMPHHALILCVWFGQFPLTRATYALRILS
HLVSYANSCVNPIVYALVSKHFRKGFRTICAGLLGRAPGRASGRVC
AAARGTHSGSVLERESSDLLHMSEAAGALRPCPGASQPCILEPCPGP
SWQGPKAGDSILTVDVA

FIG.9B

Pharmacology of Human and Rat GALR2 IC_{50} (nM)			
PEPTIDE	hGALR2	rat GALR2	hGALR1*
human galanin	3.8 ± 0.28	1.5 ± 0.45	0.13 ± 0.04
porcine galanin	1.5 ± 0.03	0.83 ± 0.5	0.14 ± 0.04
rat galanin	1.6 ± 0.42	0.9	0.1
rat Gal (2-29)	15.4 ± 7.9	2.9 ± 0.9	17 ± 7.5
rat Gal (3-29)	>1000	>1000	>1000
M40	9.5 ± 0.7	1.8 ± 1.8	0.48 ± 0.2
M35	5.6 ± 0.2	0.43 ± 0.18	0.04 ± 0.02
C7	40.5 ± 19	13.5 ± 0.7	6.3 ± 6.7
Kd	5 nM	0.19 nM	0.07 nM

FIG.10

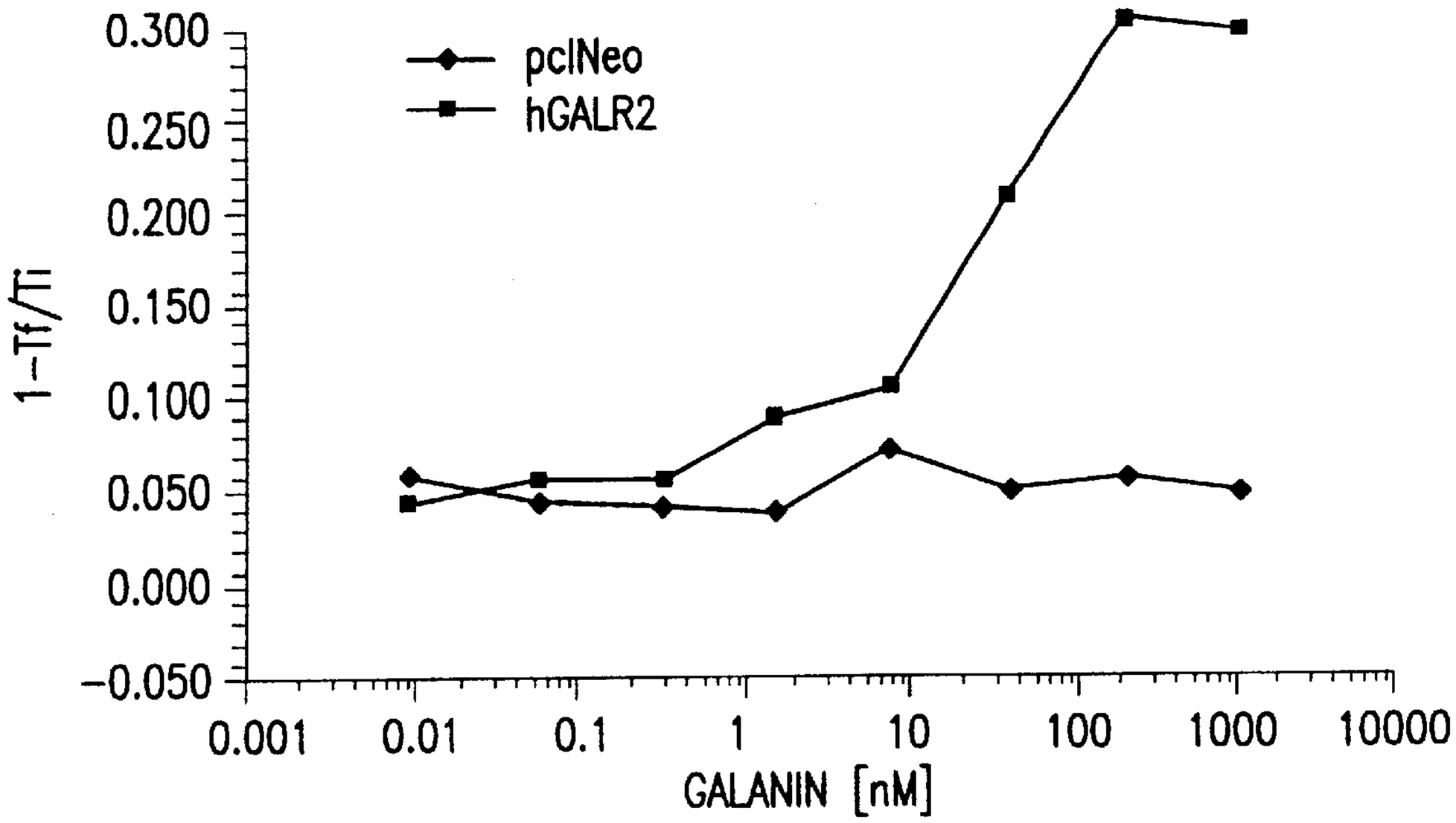

FIG.11A

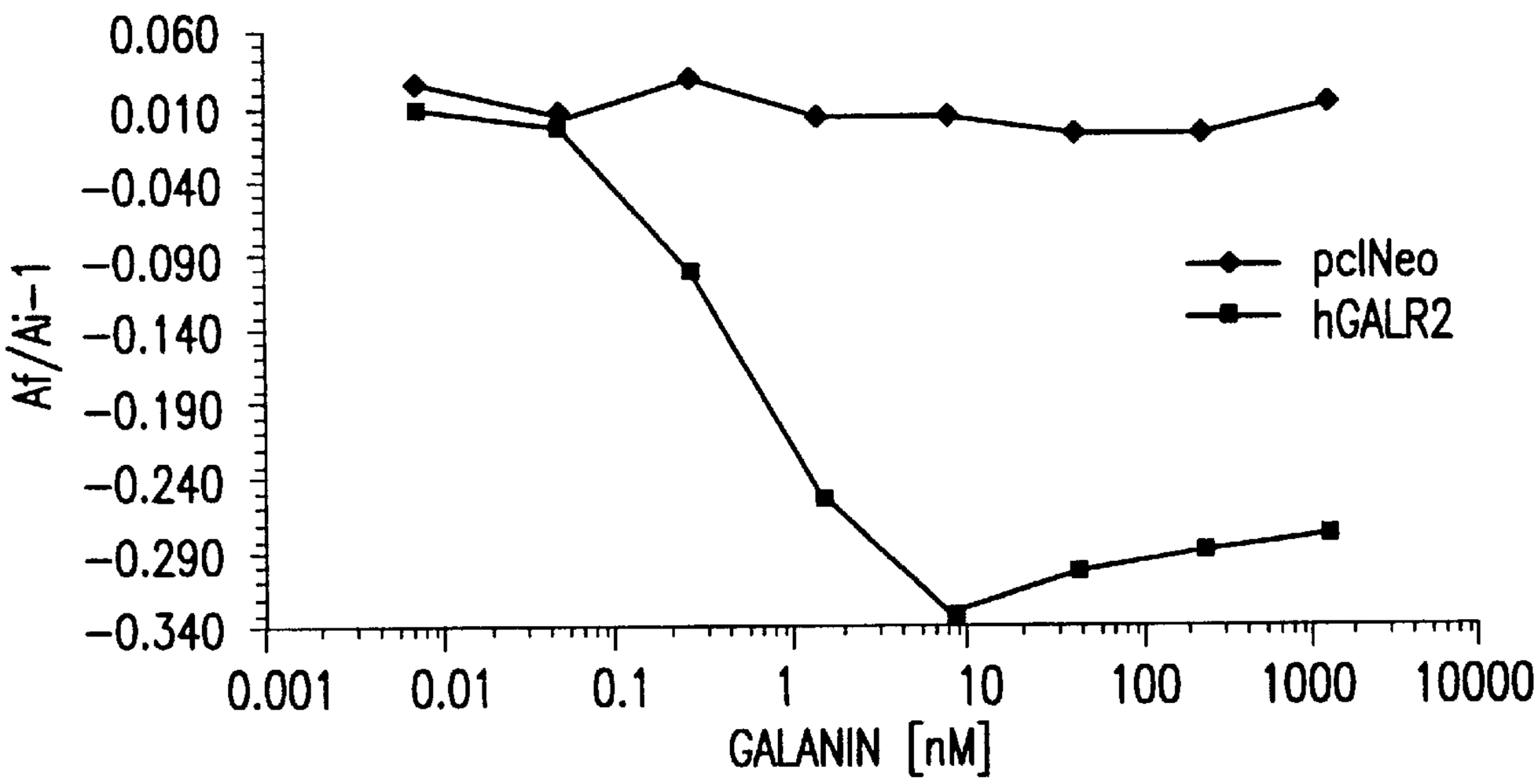

FIG.11B

gcccttccactttggtgataccATGAATGGCTCGGACAGCCAGGGGGCGGA
GGACTCGAGCCAGGAAGGTGGCGGCGGCTGGCAGCCCGAGGCG
GTCCTCGTACCCCTATTTTTCGCGCTCATCTTCCTCGTGGGCGCTG
TGGGCAACGCGCTGGTGCTGGCGGTGCTGCTGCGCGGCGGCCAG
GCGGTCAGCACCACGAACCTATTCATCCTCAACCTGGGTGTGGC
CGACCTGTGTTTCATCCTGTGCTGCGTGCCTTTCCAGGCCACCATC
TATACCCTGGACGATTGGGTGTTTGGCTCACTGCTCTGCAAGGCC
GTTCATTTCCTCATCTTCCTCACTATGCACGCCAGCAGCTTCACGC
TGGCCGCTGTCTCGCTGGACAGgtgagtgaacattctgtggtgtctgagaactgggt
acccaggtaggagcttgcactggagtcgccacgcaaggatccagaagggatgcgtagtcggggag
aacactaaaattacaaagtggcccgaggccgtgaaacgcaaggggaaaggggactaagactccg
tgactaagagtgtcccttgattaagtcggtcctcagacctcgaaggctggagaaatcggatttctgggg
tctttacgttattgttgcttgagctaaaagtctctcagaaacattgcagtactcagaccagagttggcttg
caaagtaacttgccagtattcaaatgctaattgagagctgcagagaggcatttgcttcttggccccaag
ctcagcacctggagcgttgtccggctttaggcttaggactgagctgtactttggatagacccatgctga
agtccaaggcagcgggagtgagggctcctagcggacgtctaaagccttccaggccaaggctccccg
cccggagacgcctgcggtttgatgttccttccctagctaaaggacccagaaagagaaacttccagaat
gctctgaaggactcgtgactggaaaagacactagaaacaggtcctgggaaggatgtcattagttccc
tgcccttcgcatcacttggcccttcccacagtagagcggtgaagagaggcggagatcctcattctctg
ctttccactgagtgcaacatgtgggttctgagtccgctggtgggacgcacaaaacttcagctttcttcag
ggatttccttgctctacccaagtcttctccgggttgtctgtcagagagcctcaggcattagagatttgtctc
cctcggttgtcacaagaggataataatcactgcccccagaagtcctggcatattctacaacttttagtttt
cggtggtttggggatgcccttcgcgtggtaggtcagtggccacattctcagggttggtaatggtctagc
agtgaattagtgaatcctttcgcttacctgtcgtcgtcgtccccccccgccccactgtccactcagGTAT
CTGGCCATCCGCTACCCGATGCACTCCCGAGAGTTGCGCACACCT
CGAAACGCGCTGGCGGCCATCGGGCTCATCTGGGGGCTAGCACT
GCTCTTCTCCGGGCCCTACCTGAGCTACTACAGTCAGTCGCAGCT
GGCCAATCTGACGGTGTGCCACCCAGCGTGGAGCGCACCACGAC
GTCGCGCCATGGACCTCTGCACTTTTGTCTTTAGCTACCTGTTGCC
AGTGCTGGTGCTCAGCCTGACCTATGCGCGCACCCTGCACTACCT
CTGGCGCACAGTTGACCCAGTAGCTGCAGGCTCAGGTTCCCAGC
GCGCCAAGCGCAAGGTGACACGGATGATCGTCATCGTGGCGGTA
CTCTTCTGCCTCTGTTGGATGCCCCACCACGCGCTTATCCTCTGCG
TGTGGTTTGGTCGCTTTCCGCTCACGCGTGCCACTTACGCCCTGC
GCATCCTTTCACATCTAGTATCTTATGCCAACTCGTGTGTCAACCC
CATCGTTTATGCTCTGGTCTCCAAGCATTTCCGCAAAGGTTTCCG
CAAAATCTGCGCGGGCCTGCTACGCCGTGCCCCGAGGAGAGCTT
CAGGCCGAGTGTGCATCCTGGCGCCTGGAAACCATAGTGGTGGC
ATGCTGGAACCTGAGTCCACAGACCTGACACAGGTGAGCGAGG
CAGCCGGGCCCCTCGTCCCCGCACCCGCACTTCCCAACTGCACA
ACCTTGAGTAGAACCCTCGATCCAGCCTGTTAAaggaccaaagggcatct
aacagcttctaagggcga

FIG. 12

MNGSDSQGAEDSSQEGGGGWQPEAVLVPLFFALIFLVGAVGNALVL
AVLLRGGQAVSTTNLFILNLGVADLCFILCCVPFQATIYTLDDWVFG
SLLCKAVHFLIFLTMHASSFTLAAVSLDRYLAIRYPMHSRELRTPRN
ALAAIGLIWGLALLFSGPYLSYYSQSQLANLTVCHPAWSAPRRRAM
DLCTFVFSYLLP VLVLSLTYARTLHYLWRTVDPVAAGSGSQRAKRK
VTRMIVIVAVLF CLCWMPHHALILCVWFGRFPLTRATYALRILSHL
VSYANSCVNPIVYALVSKHFRKGFRKICAGLLRRAPRRASGRVCIL
APGNHSGGMLEPESTDLTQVSEAAGPLVPAPALPNCTTLSRTLDPAC

FIG.13

```
mGALR1   1  M E L A M V N L S E G N G S D P E P P A P E S R P L F G I G V E N  33
rGALR1   1  M E L A P V N L S E G N G S D P E P P A - E P R P L F G I G V E N  32
hGALR1   1  M E L A V G N L S E G N A S C P E P P A P E P G P L F G I G V E N  33
mGALR2   1  M - - - - - N G S D S Q G A E D S S Q E G G - G - - - G W Q P E A  24
rGALR2   1  M - - - - - N G S G S Q G A E N T S Q E G G S G - - - G W Q P E A  25
hGALR2   1  M - - - - - N V S G C P G A G N A S Q A G G G G - - - G W H P E A  25

mGALR1  34  F I T L V V F G L I F A M G V L G N S L V I T V L A R S K P G K -  65
rGALR1  33  F I T L V V F G L I F A M G V L G N S L V I T V L A R S K P G K -  64
hGALR1  34  F V T L V V F G L I F A L G V L G N S L V I T V L A R S K P G K -  65
mGALR2  25  V L V P L F F A L I F L V G A V G N A L V L A V L L R G - - - - -  53
rGALR2  26  V L V P L F F A L I F L V G T V G N A L V L A V L L R G G - - - -  54
hGALR2  26  V I V P L L F A L I F L V G T V G N T L V L A V L L R G G - - - -  54

mGALR1  66  - - P R S T T N L F I L N L S I A D L A Y L L F C I P F Q A T V Y  96
rGALR1  65  - - P R S T T N L F I L N L S I A D L A Y L L F C I P F Q A T V Y  95
hGALR1  66  - - P R S T T N L F I L N L S I A D L A Y L L F C I P F Q A T V Y  96
mGALR2  54  Q A V - S T T N L F I L N L G V A D L C F I L C C V P F Q A T I Y  85
rGALR2  55  Q A V - S T T N L F I L N L G V A D L C F I L C C V P F Q A T I Y  86
hGALR2  55  Q A V - S T T N L F I L N L G V A D L C F I L C C V P F Q A T I Y  86

mGALR1  97  A L P T W V L G A F I C K F I H Y F F T V S M L V S I F T L A A M  129
rGALR1  96  A L P T W V L G A F I C K F I H Y F F T V S M L V S I F T L A A M  128
hGALR1  97  A L P T W V L G A F I C K F I H Y F F T V S M L V S I F T L A A M  129
mGALR2  86  T L D D W V F G S L L C K A V H F L I F L T M H A S S F T L A A V  118
rGALR2  87  T L D D W V F G S L L C K A V H F L I F L T M H A S S F T L A A V  119
hGALR2  87  T L D G W V F G S L L C K A V H F L I F L T M H A S S F T L A A V  119
```

FIG.14A

```
mGALR1  130  S V D R Y V A I V H S R R S S S L R V S R N A L L G V G F I W A L  162
rGALR1  129  S V D R Y V A I V H S R R S S S L R V S R N A L L G V G F I W A L  161
hGALR1  130  S V D R Y V A I V H S R R S S S L R V S R N A L L G V G C I W A L  162
mGALR2  119  S L D R Y L A I R Y P M H S R E L R T P R N A L A A I G L I W G L  151
rGALR2  120  S L D R Y L A I R Y P L H S R E L R T P R N A L A A I G L I W G L  152
hGALR2  120  S L D R Y L A I R Y P L H S R E L R T P R N A L A A I G L I W G L  152

mGALR1  163  S I A M A S P V A Y H Q R L F H - R D S N Q T F C W E Q W P N K L  194
rGALR1  162  S I A M A S P V A Y Y Q R L F H - R D S N Q T F C W E H W P N Q L  193
hGALR1  163  S I A M A S P V A Y H Q G L F H P R A S N Q T F C W E Q W P D P R  195
mGALR2  152  A L L F S G P - - Y L S Y Y S Q S Q L A N L T V C H P A W S A P R  182
rGAL2   153  A L L F S G P - - Y L S Y Y R Q S Q L A N L T V C H P A W S A P R  183
hGALR2  153  S L L F S G P - - Y L S Y Y R Q S Q L A N L T V C H P A W S A P R  183

mGALR1  195  H K K A Y V V C T F V F G Y L L P L L L I C F C Y A K V L N H L H  227
rGALR1  194  H K K A Y V V C T F V F G Y L L P L L L I C F C Y A K V L N H L H  226
hGALR1  196  H K K A Y V V C T F V F G Y L L P L L L I C F C Y A K V L N H L H  228
mGALR2  183  R R - A M D L C T F V F S Y L L P V L V L S L T Y A R T L H Y L W  214
rGALR2  184  R R - A M D L C T F V F S Y L L P V L V L S L T Y A R T L R Y L W  215
hGALR2  184  R R - A M D I C T F V F S Y L L P V L V L G L T Y A R T L R Y L W  215
```

FIG.14B

```
mGALR1 228  K K L K N M - S K K S E A S - - - K K K T A Q T V L V V V V V F G  256
rGALR1 227  K K L K N M - S K K S E A S - - - K K K T A Q T V L V V V V V F G  255
hGALR1 229  K K L K N M - S K K S E A S - - - K K K T A Q T V L V V V V V F G  257
mGALR2 215  R T V D P V - - A A G S G S Q R A K R K V T R M I V I V A V L F C  245
rGALR2 216  R T V D P V - - T A G S G S Q R A K R K V T R M I I I V A V L F C  246
hGALR2 216  R A V D P V - - A A G S G A R R A K R K V T R M I L I V A A L F C  246

mGALR1 257  I S W L P H H V V H L W A E F G A F P L T P A S F F F R I T A H C  289
rGALR1 256  I S W L P H H V I H L W A E F G A F P L T P A S F F F R I T A H C  288
hGALR1 258  I S W L P H H I I H L W A E F G V F P L T P A S F L F R I T A H C  290
mGALR2 246  L C W M P H H A L I L C V W F G R F P L T R A T Y A L R I L S H L  278
rGALR2 247  L C W M P H H A L I L C V W F G R F P L T R A T Y A L R I L S H L  279
hGALR2 247  L C W M P H H A L I L C V W F G Q F P L T R A T Y A L R I L S H L  279

mGALR1 290  L A Y S N S S V N P I I Y A F L S E N F R K A Y K Q V F K C H V C  322
rGALR1 289  L A Y S N S S V N P I I Y A F L S E N F R K A Y K Q V F K C R V C  321
hGALR1 291  L A Y S N S S V N P I I Y A F L S E N F R K A Y K Q V F K C H I R  323
mGALR2 279  V S Y A N S C V N P I V Y A L V S K H F R K G F R K I - - C A G L  309
rGALR2 280  V S Y A N S C V N P I V Y A L V S K H F R K G F R K I - - C A G L  310
hGALR2 280  V S V A N S C V N P I V Y A L V S K H F R K G F R T I - - C A G L  310

mGARL1 323  D E S P R S E T K E N K S R - - - - - - - - - - M D T P P S T N C T  346
rGALR1 322  N E S P H G D A K E - K N R - - - - - - - - - - I D T P P S T N C T  344
hGALR1 324  K D S H L S D T K E N K S R - - - - - - - - - - I D T P P S T N C T  347
mGALR2 310  L R R A P R R A S G R V C I L A P G N H S G G M L E P E S T D L T  342
rGALR2 311  L R P A P R R A S G R V S I L A P G N H S G S M L E Q E S T D L T  343
hGALR2 311  L G R A P G R A S G R V C A A A R G T H S G S V L E R E S S D L L  343
```

FIG.14C

```
mGALR1 347  H V - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - -  348
rGALR1 345  H V - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - -  346
hGALR1 348  H V - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - -  349
mGALR2 343  Q V S E A A G P L V P A P A - - - - - - L P N C T T L S R T L D P  369
rGALR2 344  Q V S E A A G P L V P P P A - - - - - - L P N C T A S S R T L D P  370
hGALR2 344  H M S E A A G A L R P C P G A S Q P C I L E P C P G P S W Q G P K  376

mGALR1   0  - - - - - - - - - - -  348
rGALR1   0  - - - - - - - - - - -  346
hGALR1   0  - - - - - - - - - - -  349
mGALR2 370  A C - - - - - - - - -  371
rGALR2 371  A C - - - - - - - - -  372
hGALR2 377  A G D S I L T V D V A  387
```

FIG. 14D

Tissue	Expression Level	Tissue	Expression Level
Total Brain	+	Prostate	+++
Cerebellum	+	Thymus	++
Cerebral Cortex	+	Spleen	+
Medulla	+	Pancreas	+
Occipital Pole	+	Placenta	++
Frontal Pole	+	Heart	-
Temporal Lobe	+	Lung	-
Putamen	+	Liver	-
Spinal Cord	+	Skeletal muscle	-
Amygdala	+	Kidney	-
Caudate Nucleus	+	Testis	-
Corpus Callosum	+	Ovary	-
Hippocampus	+	Small intestine	-
Substantia Nigra	+	Colon	-
Subthalamic n.	+	Blood Leukocyte	-
Thalamus	+		

FIG.15

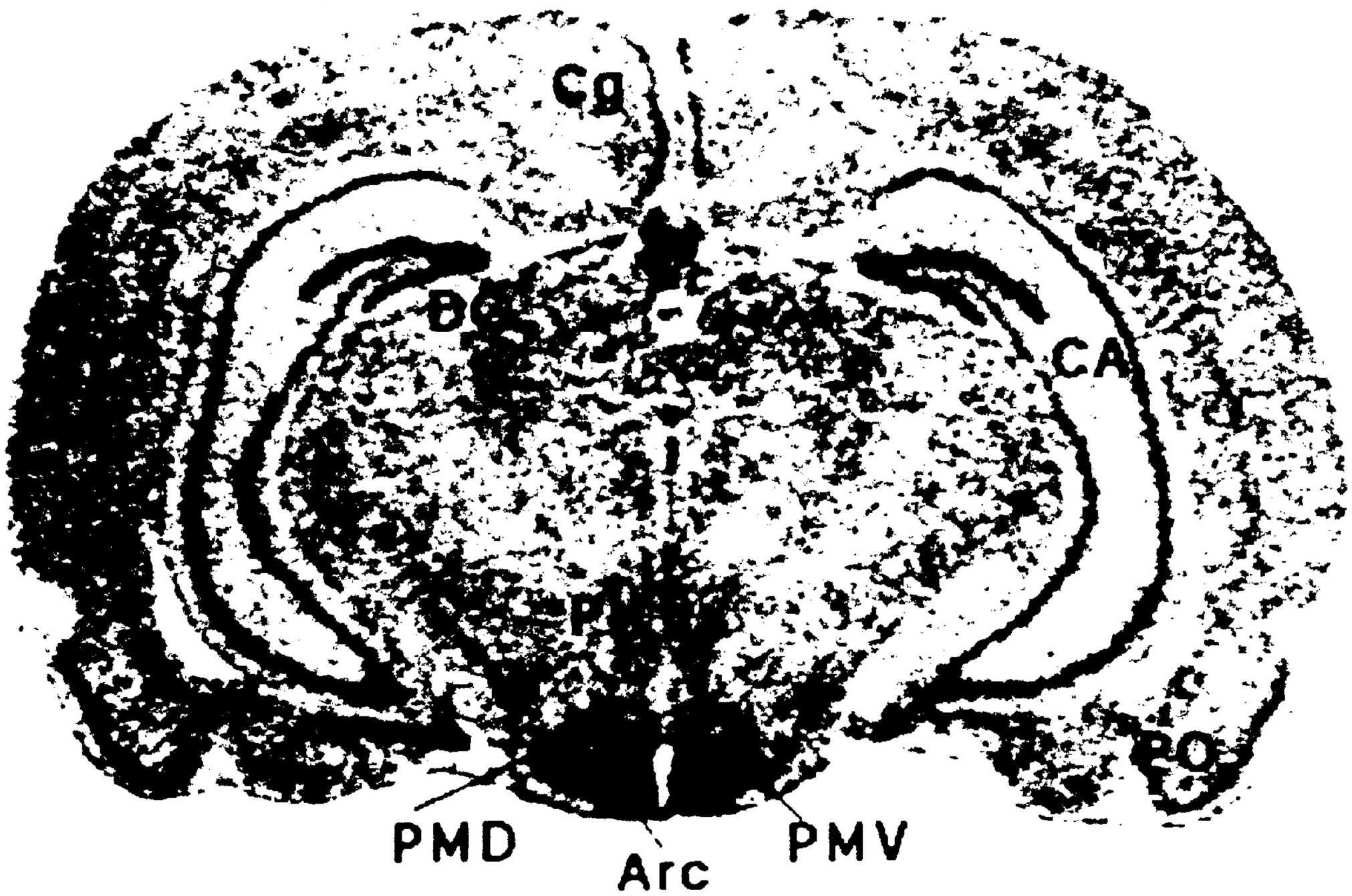

FIG.16

NUCLEIC ACID ENCODING MOUSE GALANIN RECEPTOR (GALR2)

CROSS-REFERENCE TO RELATED APPLICATIONS

The present application claims priority to application Ser. No. 60/033,851, filed Dec. 27, 1996.

STATEMENT REGARDING FEDERALLY-SPONSORED R&D

Not applicable

REFERENCE TO MICROFICHE APPENDIX

Not applicable

FIELD OF THE INVENTION

This invention relates to a novel galanin receptor, designated GALR2, to nucleotides encoding it, and to assays which use it.

BACKGROUND OF THE INVENTION

Although first isolated from porcine intestine, galanin is widely distributed in the central and peripheral nervous system. Galanin in most species is a 29 amino acid peptide with an amidated carboxyl terminus. Human galanin is unique in that it is longer, 30 amino acids, and is not amidated. There is strong conservation of the galanin sequence with the amino terminal fifteen residues being absolutely conserved in all species. Galanin immunoreactivity and binding is abundant in the hypothalamus, the locus coeruleus, the hippocampus and the anterior pituitary, as well as regions of the spinal cord, the pancreas and the gastrointestinal tract.

Like neuropeptide Y (NPY), injection of galanin into the paraventricular nucleus (PVN) of the hypothalamus produces a dose-dependent increase in feeding in satiated rats. While galanin, like norepinephrine, enhances carbohydrate ingestion, some studies have shown that it profoundly increases fat intake. It has been suggested that galanin shifts macronutrient preference from carbohydrate to fat. The same injections that increase feeding reduce energy expenditure and inhibit insulin secretion. There is enhanced galanin expression in the hypothalamus of genetically obese rats compared with their lean littermate controls. Injection of peptide receptor antagonists into the PVN blocks the galanin-specific induction of increased fat intake. Specific galanin antisense oligonucleotides when injected into the PVN produce a specific decrease in galanin expression associated with a decrease in fat ingestion and total caloric intake while hardly affecting either protein or carbohydrate intake. Thus galanin appears to be one potential neurochemical marker related to the behavior of fat ingestion.

Galanin inhibits cholinergic function and impairs working memory in rats. Lesions that destroy cholinergic neurons result in deficits in spatial learning tasks. While locally administered acetylcholine (ACh) reverses some of this deficit, galanin blocks this ACh-mediated improvement. Evidence from autopsy samples from Alzheimer's disease-afflicted brains suggests an increased galinergic innervation of the nucleus basilis. Thus, if galinergic overactivity contributes to the decline in cognitive performance in Alzheimer's disease, galanin antagonists may be therapeutically useful in alleviating cognitive impairment.

In the rat, administration of galanin intracerebroventricularly, subcutaneously or intravenously

increases plasma growth hormone. Infusion of human galanin into healthy subjects also increases plasma growth hormone and potently enhances the growth hormone response to GHRH.

Galanin levels are particularly high in dorsal root ganglia. Sciatic nerve resection dramatically up-regulates galanin peptide and mRNA levels. Chronic administration of galanin receptor antagonists (M35, M15) after axotomy results in a marked increase in self mutilation behavior in rats, generally considered to be a response to pain. Application of antisense oligonucleotides specific for galanin to the proximal end of a transected sciatic nerve suppressed the increase in galanin peptide levels with a parallel increase in autotomy. Galanin injected intrathecally acts synergistically with morphine to produce analgesia, this antinociceptive effect of morphine is blocked by galanin receptor antagonists. Thus, galanin agonists may have some utility in relieving neural pain.

The actions of galanin are mediated by high affinity galanin receptors that are coupled by pertussis toxin sensitive G_i/G_o proteins to inhibition of adenylate cyclase activity, closure of L-type Ca^{++} channels and opening of ATP-sensitive K^+ channels. Specific binding of ^{125}I-galanin (Kd approximately 1 nM) has been demonstrated in areas paralleling localization of galanin immunoreactivity: hypothalamus, ventral hippocampus, basal forebrain, spinal cord, pancreas and pituitary. In most tissues the amino terminus (GAL 1–15) is sufficient for high affinity binding and agonist activity.

Recently, a galanin receptor cDNA was isolated by expression cloning from a human Bowes melanoma cell line. (Habert-Ortoli, et al. 1994. *Proc. Nat. Acad. Sci, USA* 91: 9780–9783). This receptor, GALR1, is expressed in human fetal brain and small intestine, but little else is known of its distribution. Gal(1–16) is at least 1000 times more active than pGAL(3–29) as an inhibitor of ^{125}I-porcine galanin binding to this receptor transiently expressed in COS cells. It remains to be determined whether this receptor subtype represents the hypothalamic receptor that mediates the galanin specific feeding behavior.

It would be desirable to identify further galanin receptors so that they can be used to further characterize this biological system and to identify galanin receptor subtype selective agonists and antagonists.

SUMMARY OF THE INVENTION

This invention relates to a novel galanin receptor, designated GALR2, substantially free from associated proteins, and to GALR2-like receptors which are at least about 40% homologous and which have substantially the same biological activity. In preferred embodiments of this invention, the GALR2-like receptors are at least about 60%, and more preferably at least about 75%, and even more preferably at least about 85% homologous to a GALR2 receptor. This invention also relates specifically to rat, human and mouse GALR2, substantially free from associated proteins, and to receptors which are at least about 50% homologous and which have substantially the same biological activity.

Another aspect of this invention are primate and non-primate GALR2 proteins which are encoded by substantially the same nucleic acid sequences, but which have undergone changes in splicing or other RNA processing-derived modifications or mutagenesis-induced changes, so that the expressed protein has a homologous, but different amino acid sequence from the native forms. These variant forms may have different and/or additional functions in human and animal physiology or in vitro in cell based assays.

A further aspect of this invention are nucleic acids which encode a galanin receptor or a functional equivalent from rat, human, mouse, swine, or other species. These nucleic acids may be free from associated nucleic acids, or they may be isolated or purified. The nucleic acids which encode a receptor of this invention may be any type of nucleic acid. Preferred forms are DNAs, including genomic and cDNA, although this invention specifically includes RNAs as well. Nucleic acid constructs may also contain regions which control transcription and translation such as one or more promoter regions, termination regions, and if desired enhancer regions. The nucleic acids may be inserted into any known vector including plasmids, and used to transfect suitable host cells using techniques generally available to one of ordinary skill in the art.

Another aspect of this invention are vectors comprising nucleic acids which encode GALR2, and host cells which contain these vectors. Still another aspect of this invention is a method of making GALR2 comprising introducing a vector comprising nucleic acids encoding GALR2 into a host cell under culturing conditions.

Yet another aspect of this invention are assays for GALR2 ligands which utilize the receptors and/or nucleic acids of this invention. Preferred assays of this embodiment compare the binding of the putative GALR2 ligand to the binding of galanin to GALR2.

BRIEF DESCRIPTION OF THE DRAWINGS

FIGS. **1**A and **1**B provide is the nucleic acid sequence of rat GALR2 (clone 27A) containing 5' and 3' untranslated regions (SEQ ID NO:1).

FIGS. **2**A and **2**B provide is the nucleic acid sequence of GALR2 (clone 27A) from initiator Met to polyadenylation (positions 296–2,200 of SEQ ID NO: 1).

FIGS. **3**A and **3**B provide a schematic representation of GALR2 (clone 27A) and the nucleic acid (positions 296–1, 904 of SEQ ID NO: 1) and deduced amino acid sequence of GALR2 (clone 27A).

FIG. **4** is the deduced amino acid sequence of GALR2 (clone 27A) (SEQ ID NO: 2).

FIGS. **5**A and **5**B provide a comparison (PileUp alignment) of amino acid sequences for rat GALR1 (SEQ ID NO: 3) and rat GALR2 (SEQ ID NO:2).

FIG. **6** is the nucleic acid sequence of the cDNA probe used to isolate GALR2 (SEQ ID NO:8).

FIGS. **7**A and **7**B provide is the DNA sequence of human GALR2 gene (SEQ ID NO:5).

FIG. **8** is the DNA sequence (open reading frame only) of human GALR2 gene (SEQ ID NO:6).

FIGS. **9**A and **9**B provide the deduced amino acid sequence of human GALR2 (SEQ ID NO:7).

FIG. **10** demonstrates the pharmacology of human and rat GALR2.

FIGS. **11**A and **11**B illustrate G_q or G_s coupled response (pigment dispersion) as well as G_i-coupled response (pigment aggregation).

FIG. **12** is the DNA sequence of mouse GALR2 gene (SEQ ID NO:8).

FIG. **13** is the amino acid sequence for mouse GALR2 gene (SEQ ID NO:9).

FIGS. **14**A, **14**B, **14**C, and **14**D provide a comparison of human, rat and mouse GALR1 and GALR2 protein sequences showing strong sequence conversation among members of the GALR gene family.

FIG. **15** is the RNA expression profile of human GALR2.

FIG. **16** illustrates the expression of rat GALR2 in the brain.

DETAILED DESCRIPTION OF THE INVENTION

As used throughout the specification and claims, the following definitions apply:

"Substantially free from associated proteins" means that the receptor is at least about 90%, and preferably at least about 95% free from other cell membrane proteins which are normally found in a living mammalian cell which expresses a galanin receptor.

"Substantially free from associated nucleic acids" means that the nucleic acid is at least about 90%, and preferably at least about 95%, free from other nucleic acids which are normally found in a living mammalian cell which naturally expresses a galanin receptor gene.

"Substantially the same biological activity" means that the receptor-galanin binding constant is within 5-fold of the binding constant of GALR2 and galanin, and preferably within 2-fold of the binding constant of GALR2 and galanin.

"Stringent post-hybridizational washing conditions" means 0.1×standard saline citrate (SSC) at 65° C.

"Standard post-hybridizational washing conditions" means 6×SSC at 55° C.

"Relaxed post-hybridizational washing conditions" means 6×SSC at 30° C., or 1 to 2×SSC at 55° C.

"Functional equivalent" means that a receptor which does not have the exact same amino acid sequence of a naturally occurring GALR2 protein due to alternative splicing, deletions, mutations, or additions, but retains at least 1%, preferably 10%, and more preferably 25% of the biological activity of the naturally occurring receptor. Such derivatives will have a significant homology with a natural GALR2 and can be detected by reduced stringency hybridization with a DNA sequence obtained from a GALR2. The nucleic acid encoding a functional equivalent has at least about 60% homology at the nucleotide level to a naturally occurring receptor nucleic acid.

It has been found, in accordance with this invention, that there is a second galanin receptor, which is designated GALR2. The rat, human and mouse GALR2 sequences are given in FIGS. **4**, **9** and **13**, respectively, and are referenced in the Examples; however it is to be understood that this invention specifically includes GALR2 without regard to the species and, in particular, specifically includes rodent (including rat and mouse), rhesus, swine, chicken, cow and human. The galanin 2 receptors are highly conserved throughout species, and one of ordinary skill in the art, given the rat, human and/or mouse sequences presented herein, can easily design probes to obtain the GALR2 from other species.

GALR2 proteins contain various functional domains, including one or more domains which anchor the receptor in the cell membrane, and at least one ligand binding domain. As with many receptor proteins, it is possible to modify many of the amino acids, particularly those which are not found in the ligand binding domain, and still retain at least a percentage of the biological activity of the original receptor. Thus this invention specifically includes modified functionally equivalent GALR2s which have deleted, truncated, or mutated N-terminal portions. This invention also specifically includes modified functionally equivalent GALR2s which contain modifications and/or deletions in other domains, which are not accompanied by a loss of functional activity.

Additionally, it is possible to modify other functional domains such as those that interact with second messenger effector systems, by altering binding specificity and/or selectivity. Such functionally equivalent mutant receptors are also within the scope of this invention.

The proteins of this invention were found to have structural features which are typical of the 7-transmembrane domain (TM) containing G-protein linked receptor superfamily (GPC-R's or 7-TM receptors). Thus GALR2 proteins make up new members of the GPC-R family of receptors. The intact GALR2 of this invention was found to have the general features of GPC-R's, including seven transmembrane regions, three intra- and extracellular loops, and the GPC-R protein signature sequence. The TM domains and GPC-R protein signature sequence are noted in the protein sequences of the GALR2. Not all regions are required for functioning, and therefore this invention also comprises functional receptors which lack one or more non-essential domains.

Determination of the nucleotide sequence indicated that the GALR2 belongs to the intron-containing class of GPC-R's. Clone 27A, a precursor mRNA terminating in a poly (A) tract, encodes a 1119 bp open reading frame divided into two exons by a single intron of approximately 500 bp (FIG. **4**). Exon 1 encodes the N-terminal extracellular domain through predicted TM-3, while exon 2 encodes the second predicted extracellular loop through the C-terminal intracellular domain. A perfectly conserved splice donor site (G/gt) is found at nucleotide 368 which coincides with the second residue of the G protein-coupled receptor signature aromatic triplet, (D,E) RY.

Removal of the intron indicates that clone 27A encodes a full-length rat galanin receptor polypeptide of 372-amino acids with 7 predicted TM domains, as underlined in FIG. **4**. Searches of nucleic acid and protein sequence databases revealed that the open reading frame sequence is unique and most closely related to rat galanin 1 receptor (GALR1) with 55% nucleic acid and 38% protein sequence identity. An alignment of the protein sequences for rat GALR1 and GALR2 is given in FIG. **5**. Several conserved features ascribed to GPC-R's were also identified in the rat GALR2: the signature aromatic triplet sequence (Glu-Arg-Tyr) adjacent to TM-3, Cys-98 and Cys-153 in the first two extracellular loops capable of disulfide bonding, putative amino-terminal N-glycosylation sites (Asn-Xaa-Ser/Thr), phosphorylation sites in the carboxyl-terminus and the third cytoplasmic loop, and conserved proline residues in TM-4, 5, 6 and 7.

A second cDNA clone was isolated, termed clone 16.6, which does not contain an intron and is therefore a contiguous cDNA containing the complete open reading frame of GALR2. Like clone 27A, Clone 16.6 contains a 5' untranslated region of approximately 500 bp, a contiguous GALR2 open reading frame encoding 7-TM domains (1119 bp), a 3' untranslated region of about 320 bp, and a poly (A) tract. The open reading frame sequence is identical for clones 27A (SEQ ID NO: 18) and 16.6 except for nucleotide 109 of the open reading frame (located in predicted TM-1). Clone 27A contains a T while Clone16.6 contains a C in position 109. Thus, amino acid 37 of the GALR2 protein is phenylalanine in Clone 16.6 and isoleucine in Clone 27A. Both the DNAs of clones 27A and Clone 16.6 form aspects of this invention, as do their respective proteins.

The human GALR2 protein bears strong sequence identity and similarity to the rat GALR2 ortholog. One notable difference between the human and rat forms is the presence of an additional 15 amino acids in the C-terminal intracellular domain of human GALR2. The mouse protein sequence, as well, bears very strong identity and similarity with the GALR gene family.

This invention also relates to truncated forms of GALR2, particularly those which encompass the extracellular portion of the receptor, but lack the intracellular signaling portion of the receptor, and to nucleic acids encoding these truncated forms. Such truncated receptors are useful in various binding assays. Thus this invention specifically includes modified functionally equivalent GALR2s which have deleted, truncated, or mutated N-terminal positions. This invention also specifically includes modified functionally equivalent GALR2s including receptor chimeras which contain modifications and/or deletions in other domains, which are not accompanied by a loss of functional activity.

Additionally, it is possible to modify other functional domains such as those that interact with second messenger effector systems, by altering binding specificity and/or selectivity. Such functionally equivalent mutant receptors are also within the scope of this invention.

Assays which make up further aspects of this invention include binding assays (competition for ^{125}I-galanin binding), coupling assays (including galanin-mediated inhibition of forskolin-stimulated adenylate cyclase in cells expressing galanin receptors), measurement of galanin-stimulated calcium release in cells expressing galanin receptors (such as aequorin assays), stimulation of inward rectifying potassium channels (GIRK channels, measured by voltage changes) in cells expressing galanin receptors, and measurement of pH changes upon galanin stimulation of cells expressing galanin receptors as measured with a microphysiometer.

Host cells may be cultured under suitable conditions to produce GALR2. An expression vector containing DNA encoding the receptor may be used for expression of receptor in a recombinant host cell. Recombinant host cells may be prokaryotic or eukaryotic, including but not limited to bacteria such as *E. coli*, fungal cells such as yeast, mammalian cells including but not limited to cell lines of human, bovine, porcine, monkey and rodent origin, and insect cells including but not limited to Drosophila, Spodoptera, and silkworm derived cell lines. Cell lines derived from mammalian species which are suitable and which are commercially available include, but are not limited to, L cells L-M(TK$^-$) (ATCC CCL 1.3), L cells L-M (ATCC CCL 1.2), 293 (ATCC CRL 1573), Raji (ATCC CCL 86), CV-1 (ATCC CCL 70), COS-1 (ATCC CRL 1650), COS-7 (ATCC CRL 1651), CHO-K1 (ATCC CCL 61),3T3 (ATCC CCL 92), NIH/3T3 (ATCC CRL 1658), HeLa (ATCC CCL 2), C127I (ATCC CRL 1616), BS-C-1 (ATCC CCL 26) and MRC-5 (ATCC CCL 171).

The specificity of binding of compounds showing affinity for the receptor is shown by measuring the affinity of the compounds for cells transfected with the cloned receptor or for membranes from these cells. Expression of the cloned receptor and screening for compounds that inhibit the binding of radiolabeled ligand to these cells provides a rational way for rapid selection of compounds with high affinity for the receptor. These compounds identified by the above assays may be agonists or antagonists of the receptor and may be peptides, proteins, or non-proteinaceous organic molecules. Alternatively, functional assays of the receptor may be used to screen for compounds which affect the activity of the receptor. Such functional assays range from ex vivo muscle contraction assays to assays which determine

second messenger levels in cells expressing the receptor. The second messenger assays include, but are not limited to, assays to measure cyclic AMP or calcium levels or assays to measure adenyl cyclase activity. These compounds identified by the above assays may be agonists, antagonists, suppressors, or inducers of the receptor. The functional activity of these compounds is best assessed by using the receptor either natively expressed in tissues or cloned and exogenously expressed.

Using the assays of this invention, galanin agonists and antagonists may be identified. A galanin agonist is a compound which binds to the GALR2, such as a galanin mimetic, and produces a cellular response which is at least about equivalent to that of galanin, and which may be greater than that of galanin. Such compounds would be useful in situations where galanin insufficiency causes anorexia, or for treatment of pain.

Also using this embodiment of the assay, galanin antagonists may be identified. A galanin antagonist is a compound which can bind to the GALR2, but produces a lesser response than that of native galanin. Such compounds would be useful in the treatment of obesity.

One assay of this invention is a method of identifying a compound which modulates GALR2 receptor comprising: a) culturing cells expressing the GALR2 receptor in the presence of the compound and b) measuring GALR2 receptor activity or second messenger activity. If desired, the determined activity can be compared to a standard, such as that measured using galanin as the compound. In preferred embodiments, the cells are transformed and express the GALR2 receptor.

The consultant cDNA clone (or shorter portions of, for instance, only 15 nucleotides long) may be used to probe libraries under hybridization conditions to find other receptors which are similar enough so that the nucleic acids can hybridize, and is particularly useful for screening libraries from other species. In this step, one of ordinary skill in the art will appreciate that the hybridization conditions can vary from very stringent to relaxed. Proper temperature, salt concentrations, and buffers are well known.

The following non-limiting Examples are presented to better illustrate the invention.

EXAMPLE 1

A cDNA library from rat hypothalamus was constructed in the plasmid-based mammalian vector pcDNA-3 (InVitrogen, San Diego, Calif.). Total RNA was isolated from freshly-dissected rat hypothalami (flash-frozen in liquid nitrogen) using the RNagents total RNA isolation kit (Promega Biotech, Madison, Wis.) with a yield of approximately 0.5 mg from 1 g (wet weight) of hypothalamic tissue. Poly $(A)^+$ mRNA was selected using the Poly A tract mRNA Isolation System III (Promega Biotech) with a yield of approximately 6 μg from 0.5 μg total RNA. 3 μg of poly $(A)^+$ was then utilized as a template for cDNA synthesis using a kit (Choice Superscript, Life Technologies, Gaithersberg, Md.) with both random hexamer and oligo (dT)-Not I priming. The double-stranded cDNA was adapted for insertion into the BstXI site of pCDNA-3 using EcoRI/BstXI adapters and transformed by electroporation into the *E.coli* strain HB101. The resulting library contained approximately 750,000 primary transformants with 90% of the clones containing inserts (average size 1–2 kb). The library (approximately 700,000 cfu) was plated onto LB plates containing ampicillin and chloramphenicol and probed with a approximately 280 bp PCR fragment (SEQ ID NO:8). Hybridization was conducted at 32° C. for 18 hrs. in 5×SSPE buffer containing 50% formamide, 4×Denhardt's solution, 0.1% SDS, 10% dextran sulfate, 30 μg/ml sheared salmon-sperm DNA with 2×10^6 cpm/ml of ^{32}P-labeled probe. The probe was radiolabeled by random-priming with $[\alpha]^{32}$P-dCTP to a specific activity of greater than 10^9 dpm/μg. The filters were then washed in 1×SSC, 0.1% SDS at 55° C. and exposed to film (Kodak X-omat) for 48 hrs. Two independent positive clones were identified (clones 27A and 16.6) and subjected to further analysis.

EXAMPLE 2

Sequence Analysis of GALR2

DNA was prepared from overnight cultures using the Wizard DNA Purification System (Promega Corp., Madison, Wis.) and subjected to automated sequence analysis using the PRISM Dye Deoxy terminator cycle sequencing kit (Applied Biosystems, Foster City, Calif.) on an ABI 377 instrument. Initial sequencing primers were complementary to the T7 and SP6 promoter sites in pcDNA-3, additional primers were made complementary to the insert DNA. Database searches (Genbank, EMBL, Swiss-Prot, PIR, dEST, Prosite, dbGPCR), sequence alignments, and analysis of the galanin receptor nucleotide and protein sequences were carried out using the GCG Sequence Analysis Software Package (Madison, Wis.; pileup, peptide structure and motif programs), FASTA and BLAST search programs, and the PC/Gene software suite from Intelligenetics (San Francisco, Calif.; protein analysis programs).

EXAMPLE 3

Construction of a Vector for Expression of GALR2

Five μg of the mammalian expression vector pCI.neo (Promega Biotech, Madison Wis.) was digested with 20 units of EcoRI for 2 hours at 37° C. The digest was then treated with calf intestinal phosphatase and then electrophoresed on 1% Seaplaque gel in 1×TAE buffer and the band corresponding to linearized vector was cut out. DNA was recovered from the slice after melting at 65° C. using the Promega Wizard PCR system (Promega Biotech). DNA was quantitated by electrophoresis with standards on a 1% TBE gel. 100 ng of the 2200 bp EcoRI insert (including the intron) from pCDNA-3/27A was ligated to 50 ng of the vector pCI.neo in a 10 ml reaction at room temperature for 1 hour. 1 μl of this ligation mixture was used to transform 50 μl competent DH5a cells (Life Technologies). Clones in the correct orientation were selected following a digest with BamHI. Transfection-quality DNA was then prepared using the Qiagen Maxi protocol (Qiagen, Chatsworth, Calif.). Mammalian COS-7 cells were transfected by electroporation. COS-7 cells (1×10^7) were suspended in 0.85 ml of Ringers' buffer and 15 mg of the pCI.neo/27A clone was added to a 0.4 mm electroporation cuvette (Bio-Rad, Hercules, Calif.). Current was applied (960 μF, 260 V) using a Bio-Rad Electroporator device and the cells were transferred to a T-180 flask (Corning). Expression was allowed to proceed for 72 hrs.

EXAMPLE 4

Pharmacology of GALR2

Membranes were prepared from transfected cells following dissociation in enzyme-free dissociation solution (Specialty Media, Lavallette, N.J.) by disruption in a Dounce homogenizer in ice-cold membrane buffer (10 mM Tris, pH 7.4, 10 mM PMSF, 10 μM phosphoramidon, and 40 μg/ml bacitracin). After a low speed (1100×g for 10 min. at 4° C.) and a high speed centrifugation (38,700×g for 15 min. at 4° C.), membranes were resuspended in buffer and protein

concentration determined (Bio-Rad assay kit). Binding of ^{125}I-human galanin (specific activity of 2200 Ci/mmol, DuPont NEN) was measured in membranes using a buffer of 25 mM Tris pH 7.4, 0.5% BSA, 2 mM $MgCl_2$, 40 μg/ml bacitracin, 4 μg/ml phosphoramidon, and 10 μM leupeptin in a total volume of 250 μl. 70 pM ^{125}I-human galanin was used. Reactions were initiated by the addition of membranes and the incubation was allowed to proceed at room temperature for 1 hour. Non-specific binding was defined as the amount of radioactivity remaining bound in the presence of 1 μM cold galanin. In competition studies various concentrations of peptides (hGal, pGal, hGal(1–16), rGAL(2–29), rGAL(3–29), hGal (1–19) or chimeric peptides (C7, M15, M40, M35) were included along with ^{125}I-hGal (70 pmol). Incubations were terminated by rapid filtration through GF/C filters which had been presoaked with 0.1% polyethylamine using a TOMTEC (Orange, Conn.) cell harvester. The results were analyzed using the Prism software package (GraphPad, San Diego, Calif.). Shown in the table below is the ligand binding profiles of both rat GALR1 and rat GALR2 proteins (clone 27A shown; clone 16.6 gave similar results). The K_D for binding of ^{125}I-labeled human galanin against rat GALR2 was 0.2 nM.

	IC_{50} (nM)	
	rat GALR1	rat GALR2 (clone 27A)
pig Galanin	0.06	0.46
human Galanin	0.07 ± 0.01	1.3 ± 0.5
rat Gal (2–29)	7.2	2.9 ± 1.3
rat Gal (3–29)	>1000	>1000
human Gal (1–19)	0.86	
pig Gal (1–16)	0.27 ± 0.18	3.0
galantide(M15)	1.0 ± 1.1	28 ± 3.5
C7	4.9 ± 3	23 ± 13
M40	0.01	1.9 ± 0.14
M35	0.9 ± 0.6	0.43 ± 0.18

EXAMPLE 5

Expression of rat GALR2

In situ hybidization was conducted to map the distribution of GALR2 mRNA in rat brain using a ^{32}P-labeled GALR2 ORF fragment as a hybridization probe; see O'Dowd, B. F. et al. 1995 Genomics 28:84–91. Specific hybridization was detected in a number of brain nuclei and regions, most notably supra-, pre-(PMD/ PMV), med- and lateral mammillary nuclei, the dendate gyrus (DG), cingulate gyrus (CG), posterior hypothalamic (PH), supraoptic and arcuate nuclei (Arc) as shown in FIG. **16**. Both frontal and parietal cortical regions were also labeled.

Clone Isolation of Human GALR2; Cloning of Partial GalR2 Gene by Degenerate PCR.

Human genomic DNA was amplified by PCR using degenerate oligonucleotides designed based on the sequences encoding transmembranes (TM) regions TM3 (P1: 5' CTG ACC GYC ATG RSC ATT GAC SGC TAC, SEQ ID NO:16, wherein Y=C or T, R=A or G, S=C or G) and TM7 (P2: 5'-GGG GTT GRS GCA GCT GTT GGC RTA, SEQ ID NO: 17) of somatostatin receptors and the receptor encoded by the somatostatin-related gene, SLC-1. The PCR conditions were as follows: denaturation at 95° C. for 1 min, annealing at either 55° C., 45° C., or 38° C. for 1 min and extension at 72° C. for 2.5 min for 30 cycles, followed by a 7 min extension at 72° C. The resultant PCR products were phenol/chloroform extracted, precipitated with ethanol, phosphorylated with T4 polynucleotide kinase, and blunt-ended with Klenow enzyme. Subsequently, they were electrophoresed on a 0.5% low-melting point agarose and a fragment of the expected size was subcloned into the EcoRV site of pBluescript SK(–) (Stratagene, La Jolla, Calif.). Colonies were selected, plasmid DNA was purified, and the inserts sequenced.

EXAMPLE 6

Gene Sequence and Structure; Cloning and Sequencing of Human GalR2 Genomic DNA.

DNA fragments radiolabelled with [32P]dCTP by nick translation (Amersham) were used as a probe to screen a EMBL3 SP6/T7 human genomic library (Clontech, Palo Alto, Calif.). Positive phage clones were plaque purified, DNA was prepared, restriction enzyme digested, electrophoresed on an agarose gel, transferred to nylon membrane, and hybridized with the same probe used to screen the library, as described by Marchese et al, 1994 [Genomics 23, 609–618]. Positive phage were subcloned by digesting phage DNA, and subcloning the resultant fragment into the pBluescript vector. The DNA sequence of the clone was determined using standard methods on an ABI 372 automated sequencer (Perkin-Elmer-Applied Biosystems, Foster City, Calif.). As shown in FIG. **7**, the sequence determined shows a gene with a total of two exons interrupted by an 1800 bp intron. The deduced amino acid sequence (FIG. **9**) of the complete open reading frame (FIG. **8**) gives a protein of 387 amino acids with features typical of G protein-coupled receptors including 7 transmembrane alpha helical domains. FIG. **14** shows an alignment of GALR1 and GALR2 protein sequences with the seven transmenbrane domains underlined. The human GALR2 protein bears strong sequence identity and similarity to the rat GALR2 ortholog. One notable difference between the human and rat forms is the presence of an additional 15 amino acids in the C-terminal intracellular domain of human GALR2.

EXAMPLE 7

Receptor Expression: Human and Rat GALR2; Construction of Human GalR2 Expression Plasmid

The human GalR2 expression construct was assembled from the human genomic clone by PCR. Each exon was PCR amplified using standard conditions. The primers for exon I were: Forward, Exon I (5'-CCG GAA TTC GGT ACC ATG AAC GTC TCG GGC TGC CC-3'; SEQ ID NO:14) and Reverse, Exon I (5'-GGT AGC GGA TGG CCA GAT ACC TGT CTA GAG AGA CGG CGG CC-3'; SEQ ID NO:13). The primers for exon II were: Forward, Exon II (5'-GGC CGC CGT CTC TCT AGA CAG GTA TCT GGC CAT CCG CTA CC-3'; SEQ ID NO:14) and Reverse, Exon II (5'-GGC CGC CGT CTC TCT AGA CAG GTA TCT GGC CAT CCG CTA CC-3'; SEQ ID NO:15). PCR products were subcloned in to pBluescript and sequenced. Exon I product was subcloned into the EcoRI and XbaI sites of plasmid pCINeo (Promega, Madison, Wis.). Exon II was then cloned into the XbaI site and the orientation determined by appropriate restriction digests and DNA sequencing.

EXAMPLE 8

Radioligand Binding Assay

Plasmid DNA was prepared using the Qiagen Maxi protocol (Qiagen, Chatsworth, Calif.) and transfected into COS-7 cells by electroporation. Briefly, 0.85 μl COS-7 cells in Ringers' buffer (1.2×10^7/ml) and 20 μg of DNA were mixed in a 0.4 mm electroporation cuvette (Bio-Rad, Hercules, Calif.) and current (960 μF, 260 V) was applied using a Bio-Rad Electroporator device. Cells were transferred to a T-180 flask (Corning) with fresh media and

expression was allowed to proceed for 72 hrs. Membranes were prepared from transfected cells following disruption in enzyme-free dissociation solution (Specialty Media, Lavallette, N.J.) in a Dounce homogenizer in ice-cold membrane buffer (10 mM Tris, pH 7.4, 10 mM PMSF, 10 μM phosphoramidon, and 40 μg/ml bacitracin). After a low speed (1100×g, 10 min. at 4° C.) and a high speed centrifugation (38,700×g for 15 min. at 4° C.), membranes were suspended in buffer and the protein concentration determined (Bio-Rad assay kit). Binding of ^{125}I-human galanin (sp. act=2200 Ci/mmol, DuPont NEN) was measured in membranes using a buffer of 25 mM Tris pH 7.4, 0.5% BSA, 2 mM $MgCl_2$, 40 μg/ml bacitracin, 4 μg/ml phosphoramidon, and 10 μM leupeptin in a total volume of 0.25 ml. 70 pm ^{125}1-human galanin was used. Reactions were initiated by the addition of membranes and the incubation was allowed to proceed at room temperature for 1 hour. Non-specific binding was defined as the amount of membrane bound radioactivity remaining in the presence of 1 μM cold galanin. In competition studies various concentrations of peptides (hGal, pGal, hGal(1–16), rGAL(2–29), rGAL(3–29), hGal (1–19) or chimeric peptides (C7, M15, M40, M35) were included along with ^{125}I-hGal (70 pmol). Incubations were terminated by rapid filtration through GF/C filters which had been presoaked with 0.1% polyethylamine using a TOMTEC (Orange, Conn.) cell harvester. The results were analyzed using the Prism software package (GraphPad, San Diego, Calif.).

Recombinant expression of human GALR2 binding sites in transiently transfected COS-7 permitted the determation of pharmacology of the cloned receptor. ^{125}I-human galanin bound to the cloned GALR2 receptor with high affinity in a saturable and specific manner with a K_D of 5 nM. As summarized in FIG. **10**, competition of ^{125}I-human galanin with a variety of galanin-derived peptides and chimeric peptide antagonist/partial agonists showed that the human GALR2 receptor has a similar pharmacology of binding to that of the rat GALR2.

EXAMPLE 9

Functional Characterization; Post-receptor signalling mechanism Frog Melanophore Assay

Growth of *Xenopus laevis* melanophores and fibroblasts was performed as described previously (Potenza, M. N. et al, 1992, *Pigment Cell* Res. 3:38–43). Briefly, melanophores were grown in fibroblast-conditioned growth medium. The fibroblast-conditioned growth medium was prepared by growing fibroblasts in 70% L-15 medium (Sigma), pH 7.3, supplemented with 20% heat-inactivated fetal bovine serum (Gibco), 100 μg/ml streptomycin, 100 units/ml penicillin and 2 mM glutamine at 27.5° C. The medium from growing fibroblasts was collected, passed through a 0.2 μm filter (fibroblast-conditioned growth medium) and used to culture melanophores at 27.5° C.

Plasmid DNA was transiently transfected into melanophores by electroporation using a BTX ECM600 electroporator (Genetronics, Inc. San Diego, Calif.). Melanophores were incubated in the presence of fresh fibroblast-conditioned frog medium for 1 hour prior to harvesting of cells. Melanophore monolayers were detached by trypsinization (0.25% trypsin, JHR Biosciences), followed by inactivation of the trypsin with fibroblast-conditioned frog medium. The cells were collected by centrifugation at 200×g for 5 minutes at 4° C. Cells were washed once in fibroblast conditioned frog medium, centrifuged again and resuspended at 5×10^6 cells per ml in ice cold 70% PBS pH 7.0. 400 μl aliquots of cells in PBS were added to prechilled eppendorf tubes containing 2 μg of pcIneo:human Galanin 2 receptor plasmid DNA mixed with control receptor cDNA and naked vector DNA for a total of 20 μg DNA (2 μg each of pcDNAlamp:cannabinoid 2 and pcDNA3: thromboxane A2 receptor plasmid DNA, and 18 μg of pcDNA3.1 plasmid DNA in 40 μl total volume, or 2 μg each of pcDNA1amp: cannabinoid 2 and pcDNA3:thromboxane A2 receptor plasmid DNA, and 20 μg of pcDNA3.1 plasmid DNA in 40 μl total volume, as a control). Samples were incubated on ice for 20 min, and mixed every 7 minutes. Cell and DNA mixes were transferred to prechilled 2 mM gap electroporation cuvettes (BTX) and electroporated with the following settings: capacitance of 325 microfarad, voltage of 450 volts and resistance of 720 ohms. Immediately following electroporation, cells were mixed with fibroblast-conditioned frog medium (7.85 mls per cuvette) and plated onto flat bottom 96 well microtiter plates (NUNC). Electroporations from multiple cuvettes were pooled together prior to plating to ensure homogenous transfection efficiency. On the day following transfection, medium was removed and fresh fibroblast-conditioned frog medium was added to the melanophore monolayer and cell were incubated at 27° C.

Cells were assayed for receptor expression 2 days following transfection in 96-well plate format. On the day of ligand stimulation, medium was removed by aspiration and cells were washed with 70% L-15 containing 15 mM HEPES pH 7.3 (Sigma). Assays were dividing into two separate parts in order to examine Gs/Gq functional coupling which results in pigment dispersion in melanophores, or Gi functional coupling which results in pigment aggregation. For Gs/Gq functional coupling responses, assays were performed as follows. Cells were incubated in 100 μl of 70% L-15 containing 15 mM HEPES for 1 hour in the dark at room temperature, and then incubated in the presence of melatonin (2 nM final concentration) for 1 hour in the dark at room temperature to induce pigment aggregation. Initial absorbance at 600 nM was measured using a Bio-Tek Elx800 Microplate reader (ESBE Scientific) prior to addition of ligand. Human galanin (Peninsula) was added in duplicate wells, samples were mixed and incubated in the dark at room temperature for 1 hour, after which the final absorbance at 600 nm was determined. For Gi coupled responses, cell monolayers were incubated in the presence of 100 μl of 70% L-15 containing 2% fibroblast-conditioned growth medium, 2 mM glutamine, 100 ug/ml streptomycin, 100 units/ml penicillin and 15 mM HEPES for 15 minutes in the dark at room temperature to preset the cells to dispersion. After initial absorbance at 600 nM was determined, human galanin was added to cell monolayers, samples were mixed, incubated in the dark for 1.5 hour at room temperature and then final absorbances were determined. Absorbance readings were converted to transmission values in order to quantitate pigment dispersion using the following formula: 1–Tf/Ti, where Ti=the initial transmission at 600 nm and Tf=the final transmission at 600 nm. Pigment aggregation was quantitated using the following formula: Af/Ai–1, where Af=final absorbance at 600 nm and Ai is initial absorbance at 600 nm.

To determine whether the human GALR2 could be functionally expressed in melanophores, the expression plasmid pcIneo:hGALR2 was transiently transfected by electroporation into melanophores followed by stimulation of the transfected cells with human galanin. Increasing doses of galanin resulted in a dose-dependent dispersion of pigment in human GALR2-transfected melanophores, in contrast to control vector-transfected cells (FIG. **11**). The apparent EC_{50} for human galanin in pcIneo:hGALR2-transfected

melanophores was 20 nM, in general agreement with specific ^{125}human galanin binding in pcIneo:hGALR2-transfected COS-7 cells (IC_{50}~4 nM). The dispersion of pigment in the melanophore has been previously shown to occur either through Gαs coupling and stimulation of adenylyl cyclase or through Gαq coupling and mobilization of calcium.

There was no detectable aggregation of the pigment in either the pcIneo:hGALR2- or mock-transfected melanophores following incubation in the presence of 0.001–1000 nM human galanin. This result suggests that the hGALR2 does not couple to Gαi-mediated signaling pathways.

EXAMPLE 10

Aequorin Bioluminescence Assay

Measurement of GALR2 expression in the aequorin-expressing stable reporter cell line 293-AEQ17 (Button, D et al, 1993 "Aequorin-expressing mammalian cell lines used to report Ca^{2+} mobilization" *Cell Calcium* 14:663–671) was performed using a Luminoskan RT luminometer (Labsystems Inc., Gaithersburg, Md.) controlled by custom software written for a Macintosh PowerPC 6100. 293-AEQ17 cells (8×10^5 cells plated 18 hrs. before transfection in a T75 flask) were transfected with 22 μg of rat or human GALR2 plasmid DNA: 264 μg lipofectamine. Following approximately 40 hours of expression the apo-aequorin in the cells was charged for 4 hours with coelenterazine (10 μM) under reducing conditions (300 μM reduced glutathione) in ECB buffer (140 mM NaCl, 20 mM KCl 20 mM HEPES-NaOH [pH=7.4], 5 mM glucose, 1 mM $MgCl_2$, 1 mM $CaCl_2$, 0.1 mg/ml bovine serum albumin). The cells were harvested, washed once in ECB medium and resuspended to 500,000 cells/ml. 100 μl of cell suspension (corresponding to 5×10^4 cells) was then injected into the test plate, and the integrated light emission was recorded over 30 seconds, in 0.5 second units. 20 mL of lysis buffer (0.1% final Triton X-100 concentration) was then injected and the integrated light emission recorded over 10 seconds, in 0.5 second units. The "fractional response" values for each well were calculated by taking the ratio of the integrated response to the initial challenge to the total integrated luminescence including the Triton-X100 lysis response.

The aequorin bioluminescence assay is a reliable test for identifying G protein-coupled receptors which couple through the Ga protein subunit family consisting of Gq and G11 which leads to the activation of phospholipase C, mobilization of intracellular calcium and activation of protein kinase C. Based on the above melanophore data for GALR2, utilization of the aequorin bioluminescence assay permitted the discrimination between the two possibilities for the primary intracellular signaling mechanism for GALR2, namely Gαs coupling and stimulation of adenylyl cyclase or Gαq coupling and mobilization of calcium. Expression of human or rat GALR2 in the aequorin-expressing 293 cell line (293-AEQ17) gave a dose-dependant increase in aequorin bioluminescence in response to challenge by galanin and several related peptides. Transfection of human GALR1, which signals through Gi and the inhibition of adenylyl cyclase, gave no galanin-dependant increase in aequorin bioluminescence. Responses observed for human or rat GALR2 activation were saturable and the rank order of potency was similar to that observed for competition studies for ^{125}I-human galanin binding. EC_{50}'s, given in nM for the human GALR2 (results were similar for the rat GALR2 ortholog) were: human galanin, 32; rat galanin,12; rat galanin (2–29), 31; rat galanin (3–29)>10, 000; M35, 44; M40, 8.8. Of interest to note is that the galanin chimeric peptide antagonists (M35 and M40), thought by some to be pure antagonists on the GALR1 receptor, appear to be partial agonists on the GALR2 receptor. These data indicate that the primary signaling mechanism for GALR2 is through the phopholipase C/protein kinase C pathway, in contrast to GALR1, which communicates its intracellular signal by inhibition of adenylyl cyclase through Gi. In addition, while binding and activation of the rat and human GALR2 receptor by galanin is of high affinity and potency, rat or human GALR1 binds and is activated by galanin at a 10–30 fold lower concentration. This observation points to the existence of other undiscovered naturally-occurring ligand systems that may be agonists at the GALR2 receptor.

EXAMPLE 11

RNA Expression Profile of Human GalR2

Northern blotting analysis was utilized to assess the tissue specificity of human GALR2 mRNA expression. As shown in FIG. **15**, modest expression (indicated by one "+") is seen in a variey of brain regions and peripheral tissues, as observed for the rat ortholog of GALR2. The most prevalent transcript size is ~2.2 kb with a band of ~1.5 kb observed in spleen, thymus and prostate. Tissues with significantly higher expression levels (indicated by two or three "+") were placenta, thymus and prostate.

EXAMPLE 12

Chromosome Localization of Human GalR2 Gene

Fluorescence in situ hybridization (FISH) of metaphase spread chromosomes derived from human lymphocytes together with DAPI banding patterns was used to map hGalR2 to its chromosome, as described (Heng, H. H. Q. and Tsui, L.-C. *Modes of DAPI banding and simultaneous in situ hybridization*. Chromosoma 102:325–332). FISH data localize the receptor gene to human chromosome 17q25.

EXAMPLE 13

Mouse GALR2; Clone Isolation; Cloning of Mouse GalR2 Genomic Clone

DNA fragments from the Human GalR2 gene were radiolabelled with [32P]dCTP by random octomer labeling (Gibco BRL) and used as a probe to screen a mouse 129sv genomic library (Stratagene). Positive phage clones were plaque purified, DNA was prepared, restriction enzyme digested, electrophoresed on an agarose gel, transferred to nylon membrane, and hybridized with the same probe used to screen the library. A positive NotI fragment was subcloned into pBluescript (Stratagene).

EXAMPLE 14

Gene Sequence and Structure

DNA sequence encoding the complete ORF for mouse GALR2 (SEQ ID NO:8) is shown in FIG. **12**. A single intron of 1060 bp divides the ORF into two exons. Removal of the intron allows for conceptual translation to give the predicted GALR2 polypeptide of 371 amino acids (SEQ ID NO:9) as shown in FIG. **13**. Compared to both the human and rat orthologs, the mouse protein sequence bears strong identity (85% and 96% respectively).

SEQUENCE LISTING

(1) GENERAL INFORMATION:

(iii) NUMBER OF SEQUENCES: 18

(2) INFORMATION FOR SEQ ID NO:1:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 2200 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:

CGCTCCCTCC ACACCTCCAG GGGCAGTGAG CCACTCAAGT CTAAAGCAGA GCGAGTCCCA 60

GGACTTGAGC GCGGGAAGCG AATGGAGTCA GGGTCATTCG ATTGCACCTC TCTCGGCTGC 120

GGGCCGGAGC GGGGTACCAT CCTACACTCT GGGTGCTCCC TCCTCCTCCC GTCCCCCGCG 180

CACCCCTGCC CTGGCTCCTG GAGCTCGGCA GTCTCGCTGG GGCGCTGCAG CGAGGGAGCA 240

GCGTGCTCAC CAAGACCCGG ACAGCTGCGG GAGCGGCGTC CACTTTGGTG ATACCATGAA 300

TGGCTCCGGC AGCCAGGGCG CGGAGAACAC GAGCCAGGAA GGCGGTAGCG GCGGCTGGCA 360

GCCTGAGGCG GTCCTTGTAC CCCTATTTTT CGCGCTCATC TTCCTCGTGG GCACCGTGGG 420

CAACGCGCTG GTGCTGGCGG TGCTGCTGCG CGGCGGCCAG GCGGTCAGCA CCACCAACCT 480

GTTCATCCTC AACCTGGGCG TGGCCGACCT GTGTTTCATC CTGTGCTGCG TGCCTTTCCA 540

GGCCACCATC TACACCCTGG ACGACTGGGT GTTCGGCTCG CTGCTCTGCA AGGCTGTTCA 600

TTTCCTCATC TTTCTCACTA TGCACGCCAG CAGCTTCACG CTGGCCGCCG TCTCCCTGGA 660

CAGGTAAAGG ACCCAGAAAG AAACATCCAG TATGCCCGGA GGGATCTTGA CTGGAAAAGA 720

CTGAATCCTG GTCTGGTGAC CTTAGTTCCC TGCCCTTTCA CATCACTTGG ACATTCCCAC 780

AGAAGAGCGG TGAAGAGGCG GTGGTCCTTA TTCTCCTCTG GTTTCCACTG AGTGCAACAT 840

GTGCGTCCTG AGTACGCTGG AGGGACTCAC AAAATTTCAG CTTTCTTTAG GAGTTTCCTT 900

GCTGTAGTTT GACCCAAGTC TTCTCCAGGT TTCTGTCAGA ACCTCAGGCA TGAGGGATCT 960

GCCTCCCCTG GTTGTCACCA GAGGATAACA ATCACTGCCC CCAGAAATCC AGACAGATTC 1020

TACAACTTTT AGTCTTCGGT GTTTTGGGGG TGCCCCTTCA CGTGGAGTAG GTCGGTGGCC 1080

ACATTCCCAG GAGTGACAAT AGCCTAGCAG TGAATCCTCT CGCTTAGCTG ATGCCCCCCC 1140

ACTGTCCCCA CAGGTATCTG GCCATCCGCT ACCCGCTGCA CTCCCGAGAG TTGCGCACAC 1200

CTCGAAACGC GCTGGCCGCC ATCGGGCTCA TCTGGGGGCT AGCACTGCTC TTCTCCGGGC 1260

CCTACCTGAG CTACTACCGT CAGTCGCAGC TGGCCAACCT GACAGTATGC CACCCAGCAT 1320

GGAGCGCACC TCGACGTCGA GCCATGGACC TCTGCACCTT CGTCTTTAGC TACCTGCTGC 1380

CAGTGCTAGT CCTCAGTCTG ACCTATGCGC GTACCCTGCG CTACCTCTGG CGCACAGTCG 1440

ACCCGGTGAC TGCAGGCTCA GGTTCCCAGC GCGCCAAACG CAAGGTGACA CGGATGATCA 1500

TCATCGTGGC GGTGCTTTTC TGCCTCTGTT GGATGCCCCA CCACGCGCTT ATCCTCTGCG 1560

TGTGGTTTGG TCGCTTCCCG CTCACGCGTG CCACTTACGC GTTGCGCATC CTTTCACACC 1620

TAGTTTCCTA TGCCAACTCC TGTGTCAACC CCATCGTTTA CGCTCTGGTC TCCAAGCATT 1680

TCCGTAAAGG TTTCCGCAAA ATCTGCGCGG GCCTGCTGCG CCCTGCCCCG AGGCGAGCTT 1740

CGGGCCGAGT GAGCATCCTG GCGCCTGGGA ACCATAGTGG CAGCATGCTG GAACAGGAAT 1800

-continued

CCACAGACCT GACACAGGTG AGCGAGGCAG CCGGGCCCCT TGTCCCACCA CCCGCACTTC 1860

CCAACTGCAC AGCCTCGAGT AGAACCCTGG ATCCGGCTTG TTAAAGGACC AAAGGGCATC 1920

TAACAGCTTC TAGACAGTGT GGCCCGAGGA TCCCTGGGGG TTATGCTTGA ACGTTACAGG 1980

GTTGAGGCTA AAGACTGARG ATTGATTGTA GGGAACCTCC AGTTATTAAA CGGTGCGGAT 2040

TGCTAGAGGG TGGCATAGTC CTTCAATCCT GGCACCCGAA AAGCAGATGC AGGAGCAGGA 2100

GCAGGAGCAA AGCCAGCCAT GGAGTTTGAG GCCTGCTTGA ACTACCTGAG ATCCAATAAT 2160

AAAACATTTC ATATGCTGTG AAAAAAAAAA AAAAAAAAAA 2200

(2) INFORMATION FOR SEQ ID NO:2:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 372 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:

Met Asn Gly Ser Gly Ser Gln Gly Ala Glu Asn Thr Ser Gln Glu Gly
1 5 10 15

Gly Ser Gly Gly Trp Gln Pro Glu Ala Val Leu Val Pro Leu Phe Phe
20 25 30

Ala Leu Ile Phe Leu Val Gly Thr Val Gly Asn Ala Leu Val Leu Ala
35 40 45

Val Leu Leu Arg Gly Gly Gln Ala Val Ser Thr Thr Asn Leu Phe Ile
50 55 60

Leu Asn Leu Gly Val Ala Asp Leu Cys Phe Ile Leu Cys Cys Val Pro
65 70 75 80

Phe Gln Ala Thr Ile Tyr Thr Leu Asp Asp Trp Val Phe Gly Ser Leu
85 90 95

Leu Cys Lys Ala Val His Phe Leu Ile Phe Leu Thr Met His Ala Ser
100 105 110

Ser Phe Thr Leu Ala Ala Val Ser Leu Asp Arg Tyr Leu Ala Ile Arg
115 120 125

Tyr Pro Leu His Ser Arg Glu Leu Arg Thr Pro Arg Asn Ala Leu Ala
130 135 140

Ala Ile Gly Leu Ile Trp Gly Leu Ala Leu Leu Phe Ser Gly Pro Tyr
145 150 155 160

Leu Ser Tyr Tyr Arg Gln Ser Gln Leu Ala Asn Leu Thr Val Cys His
165 170 175

Pro Ala Trp Ser Ala Pro Arg Arg Arg Ala Met Asp Leu Cys Thr Phe
180 185 190

Val Phe Ser Tyr Leu Leu Pro Val Leu Val Leu Ser Leu Thr Tyr Ala
195 200 205

Arg Thr Leu Arg Tyr Leu Trp Arg Thr Val Asp Pro Val Thr Ala Gly
210 215 220

Ser Gly Ser Gln Arg Ala Lys Arg Lys Val Thr Arg Met Ile Ile Ile
225 230 235 240

Val Ala Val Leu Phe Cys Leu Cys Trp Met Pro His His Ala Leu Ile
245 250 255

Leu Cys Val Trp Phe Gly Arg Phe Pro Leu Thr Arg Ala Thr Tyr Ala
260 265 270

-continued

```
Leu Arg Ile Leu Ser His Leu Val Ser Tyr Ala Asn Ser Cys Val Asn
        275                 280                 285

Pro Ile Val Tyr Ala Leu Val Ser Lys His Phe Arg Lys Gly Phe Arg
    290                 295                 300

Lys Ile Cys Ala Gly Leu Leu Arg Pro Ala Pro Arg Arg Ala Ser Gly
305                 310                 315                 320

Arg Val Ser Ile Leu Ala Pro Gly Asn His Ser Gly Ser Met Leu Glu
                325                 330                 335

Gln Glu Ser Thr Asp Leu Thr Gln Val Ser Glu Ala Ala Gly Pro Leu
            340                 345                 350

Val Pro Pro Pro Ala Leu Pro Asn Cys Thr Ala Ser Ser Arg Thr Leu
        355                 360                 365

Asp Pro Ala Cys
    370
```

(2) INFORMATION FOR SEQ ID NO:3:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 346 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:3:

```
Met Glu Leu Ala Pro Val Asn Leu Ser Glu Gly Asn Gly Ser Asp Pro
 1               5                  10                  15

Glu Pro Pro Ala Glu Pro Arg Pro Leu Phe Gly Ile Gly Val Glu Asn
            20                  25                  30

Phe Ile Thr Leu Val Val Phe Gly Leu Ile Phe Ala Met Gly Val Leu
        35                  40                  45

Gly Asn Ser Leu Val Ile Thr Val Leu Ala Arg Ser Lys Pro Gly Lys
    50                  55                  60

Pro Arg Ser Thr Thr Asn Leu Phe Ile Leu Asn Leu Ser Ile Ala Asp
65                  70                  75                  80

Leu Ala Tyr Leu Leu Phe Cys Ile Pro Phe Gln Ala Thr Val Tyr Ala
                85                  90                  95

Leu Pro Thr Trp Val Leu Gly Ala Phe Ile Cys Lys Phe Ile His Tyr
            100                 105                 110

Phe Phe Thr Val Ser Met Leu Val Ser Ile Phe Thr Leu Ala Ala Met
        115                 120                 125

Ser Val Asp Arg Tyr Val Ala Ile Val His Ser Arg Arg Ser Ser Ser
    130                 135                 140

Leu Arg Val Ser Arg Asn Ala Leu Leu Gly Val Gly Phe Ile Trp Ala
145                 150                 155                 160

Leu Ser Ile Ala Met Ala Ser Pro Val Ala Tyr Tyr Gln Arg Leu Phe
                165                 170                 175

His Arg Asp Ser Asn Gln Thr Phe Cys Trp Glu His Trp Pro Asn Gln
            180                 185                 190

Leu His Lys Lys Ala Tyr Val Val Cys Thr Phe Val Phe Gly Tyr Leu
        195                 200                 205

Leu Pro Leu Leu Leu Ile Cys Phe Cys Tyr Ala Lys Val Leu Asn His
    210                 215                 220

Leu His Lys Lys Leu Lys Asn Met Ser Lys Lys Ser Glu Ala Ser Lys
225                 230                 235                 240
```

-continued

```
Lys Lys Thr Ala Gln Thr Val Leu Val Val Val Val Phe Gly Ile
                245                 250                 255

Ser Trp Leu Pro His His Val Ile His Leu Trp Ala Glu Phe Gly Ala
            260                 265                 270

Phe Pro Leu Thr Pro Ala Ser Phe Phe Phe Arg Ile Thr Ala His Cys
        275                 280                 285

Leu Ala Tyr Ser Asn Ser Ser Val Asn Pro Ile Ile Tyr Ala Phe Leu
    290                 295                 300

Ser Glu Asn Phe Arg Lys Ala Tyr Lys Gln Val Phe Lys Cys Arg Val
305                 310                 315                 320

Cys Asn Glu Ser Pro His Gly Asp Ala Lys Glu Lys Asn Arg Ile Asp
                325                 330                 335

Thr Pro Pro Ser Thr Asn Cys Thr His Val
            340                 345
```

(2) INFORMATION FOR SEQ ID NO:4:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 283 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: Other

(ix) FEATURE:
(A) NAME/KEY: Other
(B) LOCATION: 1...283
(D) OTHER INFORMATION: cDNA probe

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:4:

```
TGCGGACCAC CACCAACTTG TACCTGGGCA GCATGGCCGT GTCCGACCTA CTCATCCTGC     60

TCGGGCTGCC GTTCGACCTG TACCGCCTCT GGCGCTCGCG GCCCTGGGTG TTCGGGCCGC    120

TGCTCTGCCG CCTGTCCCTC TACGTGGGCG AGGGCTGCAC CTACGCCACG CTGCTGCACA    180

TGACCGCGCT CAGCGTCGAG CGCTACCTGG CCATCTGCCG CCCGCTCCGC GCCCGCGTCT    240

TGGTCACCCG GCGCCGCGTC CGCGCGCTCA TCGCTGTGCT CTG                      283
```

(2) INFORMATION FOR SEQ ID NO:5:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 3390 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(ix) FEATURE:
(A) NAME/KEY: Other
(B) LOCATION: 63...63
(D) OTHER INFORMATION: N = A, C, T or G
(A) NAME/KEY: Other
(B) LOCATION: 122...122
(D) OTHER INFORMATION: N = A, C, T or G

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:5:

```
GAGCTCGGAA GCAGGTACAA GCGCCACTCT CCGCCTGCGC CGTGGAATGC GCGCCGGGAC     60

CANTCCGCAG CCCTTCCCCC AGCGCCGCCG GCCGCTGCTG GGGACAACCT CGCCCTCCTG    120

TNTCTTGCTC CTCCTCCTGA CCCCAGCGCA CCCCCATCCC CGCCCCAGAT GAGGCAAGGC    180

TCCCTCCGCC TTCAGCCCGG CAGAGTCGCA CTAGGAGTTG CAGCGGCCGC AGCCCCGGGA    240

GCTTCCCGCT CGCGGAGACC CAGACGGCTG CAGGAGCCCG GGCAGCCTCG GGGTCAGCGG    300
```

-continued

CACCATGAAC GTCTCGGGCT GCCCAGGGGC CGGGAACGCG AGCCAGGCGG GCGGCGGGGG 360

AGGCTGGCAC CCCGAGGCGG TCATCGTGCC CCTGCTCTTC GCGCTCATCT TCCTCGTGGG 420

CACCGTGGGC AACACGCTGG TGCTGGCGGT GCTGCTGCGC GGCGGCCAGG CGGTCAGCAC 480

TACCAACCTG TTCATCCTTA ACCTGGGCGT GGCCGACCTG TGTTTCATCC TGTGCTGCGT 540

GCCCTTCCAG GCCACCATCT ACACCCTGGA CGGCTGGGTG TTCGGCTCGC TGCTGTGCAA 600

GGCGGTGCAC TTCCTCATCT TCCTCACCAT GCACGCCAGC AGCTTCACGC TGGCCGCCGT 660

CTCCCTGGAC AGGTGAGCCA GCGCCTTGGC CTCCCTGGGA GATGGGCATC CACGCGGGGG 720

ATGGAGCGGG AGGCGGGACT GGGGACCAAG AAGGGACGCG CAGAGTGGGA CAGGACACTA 780

AGAAGGCAGT GGAAGACAAG CGGGCGCGGA GGAGGAAAAA GAGGAATAAG AATGGGGGAC 840

CGTGGTGTCC CTCGGTTAGA TGCGTCCTGG GGCCTGGAAG CCTGGAGAAT GTGGCTCTCC 900

AGCGCCGCCC GTGCCTGACA ACGCGCAGCG TTTCCCAGTA CGACGCGTTT GTGCGCGTTC 960

ATCTCGCTTG AGCTTAATGC CCTCCGTGAG GGTGGGATAG GACAAAGTGC CCAATATACA 1020

GAAGAGTTGA GTTCCTAAGT AACTCGCTCA GAGTCGCCAG CCAAGGGATC GGGTGCGTTG 1080

AAGTGACCGT CTGTCTCCTG CAGCCAACTT CAGGCGCCTC CACTGCGCTC GCCTCCAAGC 1140

CACGGTTTGG TTGGTTGGTG CAGCTGGCTC AGGTCCAGGC TGTGGATCTT GGGTCCTTTG 1200

CAAGGATCCA CTCCGGAGTC CCAGCGAGCG TGCCTAAAGG TCCCTAGCTC AGTCCCAGCC 1260

CACTCTGCCT CTCGCCTCCA AACAAAACAA AAACAAAATA AAATCCAAAA CAAGTGGGGC 1320

GGGAGAGGAA GCGTTGCCCT GGGGTTCTTC CTCCCAGCCA GAGGAGAGCG AAGAGACGCA 1380

CATTCGGGAG AGCCGCCGGG ACTCAGGTGG AGCTTGAAAG GACACTGGGA TGGTTTCCCT 1440

GGGGAGGAAA TCCGGGTATT TCCCCTCTCC ATCCTCTGGA AAAACAGAGA GGCGAGGCCA 1500

GACTGCCCCC ACACCTCCTG TAGCCACTGA GCGCGAAGTG CGTTGGTTCC GAGCGCGCTG 1560

GTGGGATCCA CAAAGCTCGC ATTCTCTCAG GAATCCCCTG AGAAATTAAC TGTCCCTTGC 1620

CCAACATGTC TTCTCCAGGC TGTCTGCTAG AGCCTCAGGC GCCTCCGCCC TCCCTCCCGC 1680

GGCACCGTCA CCAGTGGGTA GTCACAGCCT CCCGGAGCCC ATAGCCGGTT CTCCAACCTT 1740

TAGTCTTCAG TGGCTTTGGG GTGCCCTCTC AGTGGAGACT GTGGTTGCAG TCCCCGGGGG 1800

CAGCGGGAGA ATGGCTTGAA GGCACACCTT TCCTGCTGCC GGCCCGCCCC ATTTCCAGCG 1860

TCCGCTGAGT GTCTGGGACA CGCTGGGAGG CCCCCACCTC CGCCCTCACG CCGAGCCTCA 1920

CCCCCACCTC CTCTGTGTGC GGTGTAACCA TGCGCTAAGG ACCTTCCTTG AGAGCAGCCT 1980

TGGGACCGAG GTGCAGGGGT CGCGGCCCTC CAGCATGAAT GTGCCCGCTC AGCCGACGTC 2040

TCCCTTCCCG GTCTGACCGC AGGTATCTGG CCATCCGCTA CCCGCTGCAC TCCCGCGAGC 2100

TGCGCACGCC TCGAAACGCG CTGGCAGCCA TCGGGCTCAT CTGGGGGCTG TCGCTGCTCT 2160

TCTCCGGGCC CTACCTGAGC TACTACCGCC AGTCGCAGCT GGCCAACCTG ACCGTGTGCC 2220

ATCCCGCGTG GAGCGCCCCT CGCCGCCGCG CCATGGACAT CTGCACCTTC GTCTTCAGCT 2280

ACCTGCTTCC TGTGCTGGTT CTCGGCCTGA CCTACGCGCG CACCTTGCGC TACCTCTGGC 2340

GCGCCGTCGA CCCGGTGGCC GCGGGCTCGG GTGCCCGGCG CGCCAAGCGC AAGGTGACAC 2400

GCATGATCCT CATCGTGGCC GCGCTCTTCT GCCTCTGCTG GATGCCCCAC CACGCGCTCA 2460

TCCTCTGCGT GTGGTTCGGC CAGTTCCCGC TCACGCGCGC CACTTATGCG CTTCGCATCC 2520

TCTCGCACCT GGTCTCCTAC GCCAACTCCT GCGTCAACCC CATCGTTTAC GCGCTGGTCT 2580

CCAAGCACTT CCGCAAAGGC TTCCGCACGA TCTGCGCGGG CCTGCTGGGC CGTGCCCCAG 2640

-continued

GCCGAGCCTC GGGCCGTGTG TGCGCTGCCG CGCGGGGCAC CCACAGTGGC AGCGTGTTGG 2700

AGCGCGAGTC CAGCGACCTG TTGCACATGA GCGAGGCGGC GGGGGCCCTT CGTCCCTGCC 2760

CCGGCGCTTC CCAGCCATGC ATCCTCGAGC CCTGTCCTGG CCCGTCCTGG CAGGGCCCAA 2820

AGGCAGGCGA CAGCATCCTG ACGGTTGATG TGGCCTGAAA GCACTTAGCG GGCGCGCTGG 2880

GATGTCACAG AGTTGGAGTC ATTGTTGGGG GACCGTGGGG AGAGCTTTGC CTGTTAATAA 2940

AACGCACAAA CCATTTCACA CACAGTGACA GCGCTGTTTC GCGTTTCTCA TTGTCTTGAG 3000

ATTCTGGGAG GAAGCCTCTG GGGCTTCACA GAGGGGCTCC CTAGGGGTAA GTGCAGGACC 3060

CTTTGCAGAG CTACCAGGAA AGAGGGCTGA TCACACCTCA GGCAGCCGGG TTACAATCCG 3120

CATAAAAATC TGAGTCTGGG GAGCGTGCGA CAGAGGCAGG CAGATTGTTT AAGGCGTTCG 3180

ATAAAGTCGG TTGATGACAG ACACAGATGT GTGTTCCCAG CCGCATTTGT GCTCTGGTGT 3240

GTGACAGGTC TGTCCTTGCC TGCTTTCAGC TCCCAGGGCC CCTTTGAGTC TGGGCAGCCC 3300

AGTCAGTCCC CGTCCATTTT TGGCCTTAGC TTTTCCTTCC CTGGCTACAT CTGGGCCAGG 3360

ATCAAGTCTC CAGCAGCTGT TTCACTCCCC 3390

(2) INFORMATION FOR SEQ ID NO:6:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1164 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:6:

ATGAACGTCT CGGGCTGCCC AGGGGCCGGG AACGCGAGCC AGGCGGGCGG CGGGGGAGGC 60

TGGCACCCCG AGGCGGTCAT CGTGCCCCTG CTCTTCGCGC TCATCTTCCT CGTGGGCACC 120

GTGGGCAACA CGCTGGTGCT GGCGGTGCTG CTGCGCGGCG GCCAGGCGGT CAGCACTACC 180

AACCTGTTCA TCCTTAACCT GGGCGTGGCC GACCTGTGTT TCATCCTGTG CTGCGTGCCC 240

TTCCAGGCCA CCATCTACAC CCTGGACGGC TGGGTGTTCG GCTCGCTGCT GTGCAAGGCG 300

GTGCACTTCC TCATCTTCCT CACCATGCAC GCCAGCAGCT TCACGCTGGC CGCCGTCTCC 360

CTGGACAGGT ATCTGGCCAT CCGCTACCCG CTGCACTCCC GCGAGCTGCG CACGCCTCGA 420

AACGCGCTGG CAGCCATCGG GCTCATCTGG GGGCTGTCGC TGCTCTTCTC CGGGCCCTAC 480

CTGAGCTACT ACCGCCAGTC GCAGCTGGCC AACCTGACCG TGTGCCATCC CGCGTGGAGC 540

GCCCCTCGCC GCCGCGCCAT GGACATCTGC ACCTTCGTCT TCAGCTACCT GCTTCCTGTG 600

CTGGTTCTCG GCCTGACCTA CGCGCGCACC TTGCGCTACC TCTGGCGCGC CGTCGACCCG 660

GTGGCCGCGG GCTCGGGTGC CCGGCGCGCC AAGCGCAAGG TGACACGCAT GATCCTCATC 720

GTGGCCGCGC TCTTCTGCCT CTGCTGGATG CCCCACCACG CGCTCATCCT CTGCGTGTGG 780

TTCGGCCAGT TCCCGCTCAC GCGCGCCACT TATGCGCTTC GCATCCTCTC GCACCTGGTC 840

TCCTACGCCA ACTCCTGCGT CAACCCCATC GTTTACGCGC TGGTCTCCAA GCACTTCCGC 900

AAAGGCTTCC GCACGATCTG CGCGGGCCTG CTGGGCCGTG CCCCAGGCCG AGCCTCGGGC 960

CGTGTGTGCG CTGCCGCGCG GGGCACCCAC AGTGGCAGCG TGTTGGAGCG CGAGTCCAGC 1020

GACCTGTTGC ACATGAGCGA GGCGGCGGGG GCCCTTCGTC CCTGCCCCGG CGCTTCCCAG 1080

CCATGCATCC TCGAGCCCTG TCCTGGCCCG TCCTGGCAGG GCCCAAAGGC AGGCGACAGC 1140

ATCCTGACGG TTGATGTGGC CTGA 1164

-continued

(2) INFORMATION FOR SEQ ID NO:7:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 387 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:7:

```
Met Asn Val Ser Gly Cys Pro Gly Ala Gly Asn Ala Ser Gln Ala Gly
 1               5                  10                  15

Gly Gly Gly Gly Trp His Pro Glu Ala Val Ile Val Pro Leu Leu Phe
            20                  25                  30

Ala Leu Ile Phe Leu Val Gly Thr Val Gly Asn Thr Leu Val Leu Ala
        35                  40                  45

Val Leu Leu Arg Gly Gly Gln Ala Val Ser Thr Thr Asn Leu Phe Ile
    50                  55                  60

Leu Asn Leu Gly Val Ala Asp Leu Cys Phe Ile Leu Cys Cys Val Pro
65                  70                  75                  80

Phe Gln Ala Thr Ile Tyr Thr Leu Asp Gly Trp Val Phe Gly Ser Leu
                85                  90                  95

Leu Cys Lys Ala Val His Phe Leu Ile Phe Leu Thr Met His Ala Ser
            100                 105                 110

Ser Phe Thr Leu Ala Ala Val Ser Leu Asp Arg Tyr Leu Ala Ile Arg
        115                 120                 125

Tyr Pro Leu His Ser Arg Glu Leu Arg Thr Pro Arg Asn Ala Leu Ala
    130                 135                 140

Ala Ile Gly Leu Ile Trp Gly Leu Ser Leu Leu Phe Ser Gly Pro Tyr
145                 150                 155                 160

Leu Ser Tyr Tyr Arg Gln Ser Gln Leu Ala Asn Leu Thr Val Cys His
                165                 170                 175

Pro Ala Trp Ser Ala Pro Arg Arg Arg Ala Met Asp Ile Cys Thr Phe
            180                 185                 190

Val Phe Ser Tyr Leu Leu Pro Val Leu Val Leu Gly Leu Thr Tyr Ala
        195                 200                 205

Arg Thr Leu Arg Tyr Leu Trp Arg Ala Val Asp Pro Val Ala Ala Gly
    210                 215                 220

Ser Gly Ala Arg Arg Ala Lys Arg Lys Val Thr Arg Met Ile Leu Ile
225                 230                 235                 240

Val Ala Ala Leu Phe Cys Leu Cys Trp Met Pro His His Ala Leu Ile
                245                 250                 255

Leu Cys Val Trp Phe Gly Gln Phe Pro Leu Thr Arg Ala Thr Tyr Ala
            260                 265                 270

Leu Arg Ile Leu Ser His Leu Val Ser Tyr Ala Asn Ser Cys Val Asn
        275                 280                 285

Pro Ile Val Tyr Ala Leu Val Ser Lys His Phe Arg Lys Gly Phe Arg
    290                 295                 300

Thr Ile Cys Ala Gly Leu Leu Gly Arg Ala Pro Gly Arg Ala Ser Gly
305                 310                 315                 320

Arg Val Cys Ala Ala Ala Arg Gly Thr His Ser Gly Ser Val Leu Glu
                325                 330                 335

Arg Glu Ser Ser Asp Leu Leu His Met Ser Glu Ala Ala Gly Ala Leu
            340                 345                 350
```

-continued

```
Arg Pro Cys Pro Gly Ala Ser Gln Pro Cys Ile Leu Glu Pro Cys Pro
        355                 360                 365

Gly Pro Ser Trp Gln Gly Pro Lys Ala Gly Asp Ser Ile Leu Thr Val
    370                 375                 380

Asp Val Ala
385
```

(2) INFORMATION FOR SEQ ID NO:8:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 2234 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:8:

```
GCCCTTTCCA CTTTGGTGAT ACCATGAATG GCTCGGACAG CCAGGGGGCG GAGGACTCGA     60

GCCAGGAAGG TGGCGGCGGC TGGCAGCCCG AGGCGGTCCT CGTACCCCTA TTTTTCGCGC    120

TCATCTTCCT CGTGGGCGCT GTGGGCAACG CGCTGGTGCT GGCGGTGCTG CTGCGCGGCG    180

GCCAGGCGGT CAGCACCACG AACCTATTCA TCCTCAACCT GGGTGTGGCC GACCTGTGTT    240

TCATCCTGTG CTGCGTGCCT TTCCAGGCCA CCATCTATAC CCTGGACGAT TGGGTGTTTG    300

GCTCACTGCT CTGCAAGGCC GTTCATTTCC TCATCTTCCT CACTATGCAC GCCAGCAGCT    360

TCACGCTGGC CGCTGTCTCG CTGGACAGGT GAGTGAACAT TCTGTGGTGT CTGAGAACTG    420

GGTACCCAGG TAGGAGCTTG CACTGGAGTC GCCACGCAAG GATCCAGAAG GGATGCGTAG    480

TCGGGGAGAA CACTAAAATT ACAAAGTGGC CCGAGGCCGT GAAACGCAAG GGGAAAGGGG    540

ACTAAGACTC CGTGACTAAG AGTGTCCCTT GATTAAGTCG GTCCTCAGAC CTCGAAGGCT    600

GGAGAAATCG GATTTCTGGG GTCTTTACGT TATTGTTGCT TGAGCTAAAA GTCTCTCAGA    660

AACATTGCAG TACTCAGACC AGAGTTGGCT TGCAAAGTAA CTTGCCAGTA TTCAAATGCT    720

AATTGAGAGC TGCAGAGAGG CATTTGCTTC TTGGCCCCAA GCTCAGCACC TGGAGCGTTG    780

TCCGGCTTTA GGCTTAGGAC TGAGCTGTAC TTTGGATAGA CCCATGCTGA AGTCCAAGGC    840

AGCGGGAGTG AGGGCTCCTA GCGGACGTCT AAAGCCTTCC AGGCCAAGGC TCCCCGCCCG    900

GAGACGCCTG CGGTTTGATG TTCCTTCCCT AGCTAAAGGA CCCAGAAAGA GAAACTTCCA    960

GAATGCTCTG AAGGACTCGT GACTGGAAAA GACACTAGAA ACAGGTCCTG GGAAGGATGT   1020

CATTAGTTCC CTGCCCCTTC GCATCACTTG GCCCTTCCCA CAGTAGAGCG GTGAAGAGAG   1080

GCGGAGATCC TCATTCTCTG CTTTCCACTG AGTGCAACAT GTGGGTTCTG AGTCCGCTGG   1140

TGGGACGCAC AAAACTTCAG CTTTCTTCAG GGATTTCCTT GCTCTACCCA AGTCTTCTCC   1200

GGGTTGTCTG TCAGAGAGCC TCAGGCATTA GAGATTTGTC TCCCTCGGTT GTCACAAGAG   1260

GATAATAATC ACTGCCCCCA GAAGTCCTGG CATATTCTAC AACTTTTAGT TTTCGGTGGT   1320

TTGGGGATGC CCTTTCGCGT GGTAGGTCAG TGGCCACATT CTCAGGGTTG GTAATGGTCT   1380

AGCAGTGAAT TAGTGAATCC TTTCGCTTAC CTGTCGTCGT CGTCCCCCCC GCCCCACTGT   1440

CCACTCAGGT ATCTGGCCAT CCGCTACCCG ATGCACTCCC GAGAGTTGCG CACACCTCGA   1500

AACGCGCTGG CGGCCATCGG GCTCATCTGG GGGCTAGCAC TGCTCTTCTC CGGGCCCTAC   1560

CTGAGCTACT ACAGTCAGTC GCAGCTGGCC AATCTGACGG TGTGCCACCC AGCGTGGAGC   1620

GCACCACGAC GTCGCGCCAT GGACCTCTGC ACTTTTGTCT TTAGCTACCT GTTGCCAGTG   1680

CTGGTGCTCA GCCTGACCTA TGCGCGCACC CTGCACTACC TCTGGCGCAC AGTTGACCCA   1740
```

-continued

GTAGCTGCAG GCTCAGGTTC CCAGCGCGCC AAGCGCAAGG TGACACGGAT GATCGTCATC 1800

GTGGCGGTAC TCTTCTGCCT CTGTTGGATG CCCCACCACG CGCTTATCCT CTGCGTGTGG 1860

TTTGGTCGCT TTCCGCTCAC GCGTGCCACT TACGCCCTGC GCATCCTTTC ACATCTAGTA 1920

TCTTATGCCA ACTCGTGTGT CAACCCCATC GTTTATGCTC TGGTCTCCAA GCATTTCCGC 1980

AAAGGTTTCC GCAAAATCTG CGCGGGCCTG CTACGCCGTG CCCCGAGGAG AGCTTCAGGC 2040

CGAGTGTGCA TCCTGGCGCC TGGAAACCAT AGTGGTGGCA TGCTGGAACC TGAGTCCACA 2100

GACCTGACAC AGGTGAGCGA GGCAGCCGGG CCCCTCGTCC CCGCACCCGC ACTTCCCAAC 2160

TGCACAACCT TGAGTAGAAC CCTCGATCCA GCCTGTTAAA GGACCAAAGG GCATCTAACA 2220

GCTTCTAAGG GCGA 2234

(2) INFORMATION FOR SEQ ID NO:9:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 371 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:9:

Met Asn Gly Ser Asp Ser Gln Gly Ala Glu Asp Ser Ser Gln Glu Gly
1 5 10 15

Gly Gly Gly Trp Gln Pro Glu Ala Val Leu Val Pro Leu Phe Phe Ala
20 25 30

Leu Ile Phe Leu Val Gly Ala Val Gly Asn Ala Leu Val Leu Ala Val
35 40 45

Leu Leu Arg Gly Gly Gln Ala Val Ser Thr Thr Asn Leu Phe Ile Leu
50 55 60

Asn Leu Gly Val Ala Asp Leu Cys Phe Ile Leu Cys Cys Val Pro Phe
65 70 75 80

Gln Ala Thr Ile Tyr Thr Leu Asp Asp Trp Val Phe Gly Ser Leu Leu
85 90 95

Cys Lys Ala Val His Phe Leu Ile Phe Leu Thr Met His Ala Ser Ser
100 105 110

Phe Thr Leu Ala Ala Val Ser Leu Asp Arg Tyr Leu Ala Ile Arg Tyr
115 120 125

Pro Met His Ser Arg Glu Leu Arg Thr Pro Arg Asn Ala Leu Ala Ala
130 135 140

Ile Gly Leu Ile Trp Gly Leu Ala Leu Leu Phe Ser Gly Pro Tyr Leu
145 150 155 160

Ser Tyr Tyr Ser Gln Ser Gln Leu Ala Asn Leu Thr Val Cys His Pro
165 170 175

Ala Trp Ser Ala Pro Arg Arg Arg Ala Met Asp Leu Cys Thr Phe Val
180 185 190

Phe Ser Tyr Leu Leu Pro Val Leu Val Leu Ser Leu Thr Tyr Ala Arg
195 200 205

Thr Leu His Tyr Leu Trp Arg Thr Val Asp Pro Val Ala Ala Gly Ser
210 215 220

Gly Ser Gln Arg Ala Lys Arg Lys Val Thr Arg Met Ile Val Ile Val
225 230 235 240

Ala Val Leu Phe Cys Leu Cys Trp Met Pro His His Ala Leu Ile Leu
245 250 255

-continued

```
Cys Val Trp Phe Gly Arg Phe Pro Leu Thr Arg Ala Thr Tyr Ala Leu
            260                 265                 270

Arg Ile Leu Ser His Leu Val Ser Tyr Ala Asn Ser Cys Val Asn Pro
        275                 280                 285

Ile Val Tyr Ala Leu Val Ser Lys His Phe Arg Lys Gly Phe Arg Lys
    290                 295                 300

Ile Cys Ala Gly Leu Leu Arg Arg Ala Pro Arg Arg Ala Ser Gly Arg
305                 310                 315                 320

Val Cys Ile Leu Ala Pro Gly Asn His Ser Gly Gly Met Leu Glu Pro
                325                 330                 335

Glu Ser Thr Asp Leu Thr Gln Val Ser Glu Ala Ala Gly Pro Leu Val
            340                 345                 350

Pro Ala Pro Ala Leu Pro Asn Cys Thr Thr Leu Ser Arg Thr Leu Asp
        355                 360                 365

Pro Ala Cys
    370
```

(2) INFORMATION FOR SEQ ID NO:10:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 348 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:10:

```
Met Glu Leu Ala Met Val Asn Leu Ser Glu Gly Asn Gly Ser Asp Pro
 1               5                  10                  15

Glu Pro Pro Ala Pro Glu Ser Arg Pro Leu Phe Gly Ile Gly Val Glu
            20                  25                  30

Asn Phe Ile Thr Leu Val Val Phe Gly Leu Ile Phe Ala Met Gly Val
        35                  40                  45

Leu Gly Asn Ser Leu Val Ile Thr Val Leu Ala Arg Ser Lys Pro Gly
    50                  55                  60

Lys Pro Arg Ser Thr Thr Asn Leu Phe Ile Leu Asn Leu Ser Ile Ala
65                  70                  75                  80

Asp Leu Ala Tyr Leu Leu Phe Cys Ile Pro Phe Gln Ala Thr Val Tyr
                85                  90                  95

Ala Leu Pro Thr Trp Val Leu Gly Ala Phe Ile Cys Lys Phe Ile His
            100                 105                 110

Tyr Phe Phe Thr Val Ser Met Leu Val Ser Ile Phe Thr Leu Ala Ala
        115                 120                 125

Met Ser Val Asp Arg Tyr Val Ala Ile Val His Ser Arg Arg Ser Ser
    130                 135                 140

Ser Leu Arg Val Ser Arg Asn Ala Leu Leu Gly Val Gly Phe Ile Trp
145                 150                 155                 160

Ala Leu Ser Ile Ala Met Ala Ser Pro Val Ala Tyr His Gln Arg Leu
                165                 170                 175

Phe His Arg Asp Ser Asn Gln Thr Phe Cys Trp Glu Gln Trp Pro Asn
            180                 185                 190

Lys Leu His Lys Lys Ala Tyr Val Val Cys Thr Phe Val Phe Gly Tyr
        195                 200                 205

Leu Leu Pro Leu Leu Leu Ile Cys Phe Cys Tyr Ala Lys Val Leu Asn
    210                 215                 220
```

-continued

```
His Leu His Lys Lys Leu Lys Asn Met Ser Lys Lys Ser Glu Ala Ser
225                 230                 235                 240

Lys Lys Lys Thr Ala Gln Thr Val Leu Val Val Val Val Phe Gly
                245                 250                 255

Ile Ser Trp Leu Pro His His Val Val His Leu Trp Ala Glu Phe Gly
            260                 265                 270

Ala Phe Pro Leu Thr Pro Ala Ser Phe Phe Phe Arg Ile Thr Ala His
        275                 280                 285

Cys Leu Ala Tyr Ser Asn Ser Ser Val Asn Pro Ile Ile Tyr Ala Phe
    290                 295                 300

Leu Ser Glu Asn Phe Arg Lys Ala Tyr Lys Gln Val Phe Lys Cys His
305                 310                 315                 320

Val Cys Asp Glu Ser Pro Arg Ser Glu Thr Lys Glu Asn Lys Ser Arg
                325                 330                 335

Met Asp Thr Pro Pro Ser Thr Asn Cys Thr His Val
            340                 345
```

(2) INFORMATION FOR SEQ ID NO:11:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 349 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:11:

```
Met Glu Leu Ala Val Gly Asn Leu Ser Glu Gly Asn Ala Ser Cys Pro
 1               5                  10                  15

Glu Pro Pro Ala Pro Glu Pro Gly Pro Leu Phe Gly Ile Gly Val Glu
            20                  25                  30

Asn Phe Val Thr Leu Val Val Phe Gly Leu Ile Phe Ala Leu Gly Val
        35                  40                  45

Leu Gly Asn Ser Leu Val Ile Thr Val Leu Ala Arg Ser Lys Pro Gly
    50                  55                  60

Lys Pro Arg Ser Thr Thr Asn Leu Phe Ile Leu Asn Leu Ser Ile Ala
65                  70                  75                  80

Asp Leu Ala Tyr Leu Leu Phe Cys Ile Pro Phe Gln Ala Thr Val Tyr
                85                  90                  95

Ala Leu Pro Thr Trp Val Leu Gly Ala Phe Ile Cys Lys Phe Ile His
            100                 105                 110

Tyr Phe Phe Thr Val Ser Met Leu Val Ser Ile Phe Thr Leu Ala Ala
        115                 120                 125

Met Ser Val Asp Arg Tyr Val Ala Ile Val His Ser Arg Arg Ser Ser
    130                 135                 140

Ser Leu Arg Val Ser Arg Asn Ala Leu Leu Gly Val Gly Cys Ile Trp
145                 150                 155                 160

Ala Leu Ser Ile Ala Met Ala Ser Pro Val Ala Tyr His Gln Gly Leu
                165                 170                 175

Phe His Pro Arg Ala Ser Asn Gln Thr Phe Cys Trp Glu Gln Trp Pro
            180                 185                 190

Asp Pro Arg His Lys Lys Ala Tyr Val Val Cys Thr Phe Val Phe Gly
        195                 200                 205

Tyr Leu Leu Pro Leu Leu Leu Ile Cys Phe Cys Tyr Ala Lys Val Leu
    210                 215                 220
```

-continued

```
Asn His Leu His Lys Lys Leu Lys Asn Met Ser Lys Lys Ser Glu Ala
225                 230                 235                 240

Ser Lys Lys Lys Thr Ala Gln Thr Val Leu Val Val Val Val Val Phe
                245                 250                 255

Gly Ile Ser Trp Leu Pro His His Ile Ile His Leu Trp Ala Glu Phe
            260                 265                 270

Gly Val Phe Pro Leu Thr Pro Ala Ser Phe Leu Phe Arg Ile Thr Ala
        275                 280                 285

His Cys Leu Ala Tyr Ser Asn Ser Ser Val Asn Pro Ile Ile Tyr Ala
    290                 295                 300

Phe Leu Ser Glu Asn Phe Arg Lys Ala Tyr Lys Gln Val Phe Lys Cys
305                 310                 315                 320

His Ile Arg Lys Asp Ser His Leu Ser Asp Thr Lys Glu Asn Lys Ser
                325                 330                 335

Arg Ile Asp Thr Pro Pro Ser Thr Asn Cys Thr His Val
            340                 345
```

(2) INFORMATION FOR SEQ ID NO:12:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 35 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: Other

(ix) FEATURE:
(A) NAME/KEY: Other
(B) LOCATION: 1...35
(D) OTHER INFORMATION: PCR primer

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:12:

```
CCGGAATTCG GTACCATGAA CGTCTCGGGC TGCCC                              35
```

(2) INFORMATION FOR SEQ ID NO:13:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 41 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: Other

(ix) FEATURE:
(A) NAME/KEY: Other
(B) LOCATION: 1...41
(D) OTHER INFORMATION: PCR primer

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:13:

```
GGTAGCGGAT GGCCAGATAC CTGTCTAGAG AGACGGCGGC C                       41
```

(2) INFORMATION FOR SEQ ID NO:14:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 41 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: Other

(ix) FEATURE:
(A) NAME/KEY: Other
(B) LOCATION: 1...41

-continued

(D) OTHER INFORMATION: PCR primer

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:14:

GGCCGCCGTC TCTCTAGACA GGTATCTGGC CATCCGCTAC C 41

(2) INFORMATION FOR SEQ ID NO:15:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 41 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: Other

(ix) FEATURE:
(A) NAME/KEY: Other
(B) LOCATION: 1...41
(D) OTHER INFORMATION: PCR primer

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:15:

GGCCGCCGTC TCTCTAGACA GGTATCTGGC CATCCGCTAC C 41

(2) INFORMATION FOR SEQ ID NO:16:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 27 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: Other

(ix) FEATURE:
(A) NAME/KEY: Other
(B) LOCATION: 1...27
(D) OTHER INFORMATION: PCR primer

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:16:

CTGACCGYCA TGRSCATTGA CSGCTAC 27

(2) INFORMATION FOR SEQ ID NO:17:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 24 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: Other

(ix) FEATURE:
(A) NAME/KEY: Other
(B) LOCATION: 1...24
(D) OTHER INFORMATION: PCR primer

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:17:

GGGGTTGRSG CAGCTGTTGG CRTA 24

(2) INFORMATION FOR SEQ ID NO:18:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1116 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:18:

-continued

```
ATGAATGGCT CCGGCAGCCA GGGCGCGGAG AACACGAGCC AGGAAGGCGG TAGCGGCGGC     60

TGGCAGCCTG AGGCGGTCCT TGTACCCCTA TTTTTCGCGC TCATCTTCCT CGTGGGCACC    120

GTGGGCAACG CGCTGGTGCT GGCGGTGCTG CTGCGCGGCG GCCAGGCGGT CAGCACCACC    180

AACCTGTTCA TCCTCAACCT GGGCGTGGCC GACCTGTGTT TCATCCTGTG CTGCGTGCCT    240

TTCCAGGCCA CCATCTACAC CCTGGACGAC TGGGTGTTCG GCTCGCTGCT CTGCAAGGCT    300

GTTCATTTCC TCATCTTTCT CACTATGCAC GCCAGCAGCT TCACGCTGGC CGCCGTCTCC    360

CTGGACAGGT ATCTGGCCAT CCGCTACCCG CTGCACTCCC GAGAGTTGCG CACACCTCGA    420

AACGCGCTGG CCGCCATCGG GCTCATCTGG GGGCTAGCAC TGCTCTTCTC CGGGCCCTAC    480

CTGAGCTACT ACCGTCAGTC GCAGCTGGCC AACCTGACAG TATGCCACCC AGCATGGAGC    540

GCACCTCGAC GTCGAGCCAT GGACCTCTGC ACCTTCGTCT TTAGCTACCT GCTGCCAGTG    600

CTAGTCCTCA GTCTGACCTA TGCGCGTACC CTGCGCTACC TCTGGCGCAC AGTCGACCCG    660

GTGACTGCAG GCTCAGGTTC CCAGCGCGCC AAACGCAAGG TGACACGGAT GATCATCATC    720

GTGGCGGTGC TTTTCTGCCT CTGTTGGATG CCCCACCACG CGCTTATCCT CTGCGTGTGG    780

TTTGGTCGCT TCCCGCTCAC GCGTGCCACT TACGCGTTGC GCATCCTTTC ACACCTAGTT    840

TCCTATGCCA ACTCCTGTGT CAACCCCATC GTTTACGCTC TGGTCTCCAA GCATTTCCGT    900

AAAGGTTTCC GCAAAATCTG CGCGGGCCTG CTGCGCCCTG CCCCGAGGCG AGCTTCGGGC    960

CGAGTGAGCA TCCTGGCGCC TGGGAACCAT AGTGGCAGCA TGCTGGAACA GGAATCCACA   1020

GACCTGACAC AGGTGAGCGA GGCAGCCGGG CCCCTTGTCC CACCACCCGC ACTTCCCAAC   1080

TGCACAGCCT CGAGTAGAAC CCTGGATCCG GCTTGT                              1116
```

What is claimed:

1. A nucleic acid, substantially free from associated nucleic acids, which encodes mouse GALR2 comprising the nucleotide sequence of SEQ ID NO: 8.

2. A vector comprising the nucleic acid of claim **1**.

3. A host cell comprising the vector of claim **2**.

4. A nucleic acid encoding mouse GALR2, substantially free from associated nucleic acids, comprising a nucleotide sequence encoding for the amino acid sequence of SEQ ID NO 9.

5. A vector comprising a nucleotide sequence encoding for the amino acid sequence of SEQ ID NO 9.

6. A cell comprising the vector of claim **5**.

* * * * *